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Association between Some Reproductive Hormones and Breast Cancer Progression in Premenopausal Women

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Abstract:

Breast cancer (BC) grows in a hormone-rich environment, which affected its clinical behaviour and biological features. In premenopausal women, BC tends to be detected in advanced stages and this may be a consequence of that young women are not the screening programs focus. This study aimed to evaluate the association between reproductive-related hormones: Circulating follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and progesterone (PRG) and BC progression worse outcomes. Circulating hormones levels were measured in 100 premenopausal BC patients and 40 age-matched healthy women. Results revealed that there was no significant difference in the serum level of FSH (P=0.486), LH (P=0.806), PRL (P=0.081) and PRG (P=0.474) hormones between BC cases and healthy controls. Moreover, in premenopausal BC patients, these reproductive hormones were also not significantly (P>0.05) influenced the disease progression including tumor late stages, lymph node invasion, distant metastasis, high grades, large size, negative progesterone and estrogen receptors and negative HER2 status. In conclusion, circulating FSH, LH, PRG and PRL levels seem to be not associated with BC development and/or progression. This is very important knowledge that the BC and its possible progression have no effect on the reproductive hormones and consequently on the young women fertility.

Keywords: *Breast cancer; FSH; LH; Prolactin; Progesterone.*

1. Introduction

Breast cancer (BC) is a cancerous growth that begins in the lining cells of the lobules or ducts within the breast glandular tissue **(Aslam *et al.*, 2024)**. It is the 2nd most frequent tumor and the leading cause of cancer related mortality for females, responsible for 685000 related-deaths globally in 2020 **(Zhu *et al.*, 2023)**. Particularly in women <40 years old, BC is the 2nd leading cause of cancer-related death and its incidence in young women (BCYW) has been increasing **(Zhu *et al.*, 2023)**. In young women, BC tends to be detected in more late stages and this may be a consequence of that young women are not the screening programs focus **(Costa *et al.*, 2024)**. Thus, compared to old patients, such cases have treatment complications and worse clinical outcomes **(Zhu *et al.*, 2023; Costa *et al.*, 2024)**.

BC at woman's life early phase presents several specific medical, social, and personal challenges, most of which do not apply to women who develop BC at an older age **(Kumar *et al.*, 2022)**. Compared to BC in older patients, the prognosis, curability and outcome of BCYW are worse, with a higher incidence of recurrence. This is may be owing to the BCYW detection in advanced disease stages when it has already transitioned into more aggressive behaviours **(Kumar *et al.*, 2022; Paluch-Shimon *et al.*, 2022)**. Thus, it is very important to evaluate factors significantly influence BC outcomes in premenopausal young BC patients.

About 80% of BC newly discovered instances are hormone-dependent. These hormones were reported to stimulate the tumors spread and growth **(Tavčar Kunstič *et al.*, 2023)**. In this context, preliminary studies point to luteinizing hormone (LH) potential role in tumorigenesis. In BC cells, this hormone controls cell invasion and migration that exhibit functional LH receptors **(Mondaca *et al.*, 2020)**. Besides its stimulation for mammary glands growth, prolactin (PRL) has a significant role in developing BC and other hormonally sensitive tumors such as endometrial, ovarian, lung and pancreatic cancers **(Karayazi Atıcı *et al.*, 2021)**. Based on results of a meta-analysis, the increased levels of PRL are correlated positively with BC development **(Aranha *et al.*, 2022)**. From another hand, follicle-stimulating hormone (FSH) and its receptor (FSHR) have an important function in several tumors, including ovarian **(Chen *et al.*, 2009)**, endometrial **(Davies *et al.*, 2000)** and prostate **(Ben-Josef *et al.*, 1999)** cancer. Its binding with the receptor stimulates tumor cell differentiation, proliferation, and metastasis **(Wayne *et al.*, 2007)**. FSHR expression has not been found in BC primary tissues, however, increased FSH concentrations that have

been related to significant poor prognosis in premenopausal BC cases **(Zhou *et al.*, 2013)**. Moreover, progesterone (PRG) also may have a function in BC etiology, and, to cure or prevent BC, there is interest in decreasing progesterone activity **(Trabert *et al.*, 2020)**.

Few studies were interested in studying the association between these reproductive-related hormones (FSH, LH, PRL and PRG) and BC progression and worse outcomes. As a result, this study aimed to evaluate these hormones profile in premenopausal BC patients comparing to age-matched healthy women. It is also aimed to determine whether these hormones affects BC severity including advanced stages, high histological grade, large tumor size, lymph node invasion, distant metastasis and negative expression of progesterone and estrogen receptors and HER2 protein.

2. Materials and methods

2.1. Patients and controls

The study cohort consists of 140 eligible female Egyptian women (100 premenopausal patients with primary BC and 40 age-matched healthy women). They were collected and examined clinically, radiologically and pathologically in Mansoura University Oncology Centre, Egypt. None of the healthy participants had malignancy history. Cancer features were registered based on the international Tumor-Node-Metastasis (TNM) classification system **(Greene, 2003)**. Before starting any specific treatments and after informed consent, clinicopathologic data and serum samples were collected from all patients. This study was conducted in accordance with ethical guidelines of 1975 Helsinki Declaration and was approved by the Ethics and Scientifc Comittees of Mansoura University, Egypt.

2.2. Biochemical measurements

At room temperature and after fasting for about 6-8 hours, blood samples were obtained from all participants and were centrifuged at 15 minutes, 4000 rpm. Consequently, serum was separated and stored at -20°C until use. Another blood part treated with EDTA-K3 was used for complete blood count using automated analyzer (Sysmex, Japan). In a fully automatic closed biochemistry analyser (BA200, Bio Systems, Barcelona, Spain), fresh serum samples were tested for alanine and aspartate aminotransferase (ALT and AST), bilirubin, albumin, urea and creatinine using commercial kits provided by the manufacture. By commercial ELISA assay kits, CA 15.3 and CEA (MyBioSource, San Diego, USA) according to the industrial prescript.

2.3. Reproductive hormones analysis

According to the manufacturer's instructions, serum levels of FSH, LH, PRL, and PRG were determined using chemiluminescence assay (CLIA; Maglumi 800, Snibe, Shenzhen, China). For all hormones, intra- and inter-assay variation were <3%. To each test sample condition (case/control), the laboratory technician who performed measurements was blinded.

2.4. Statistical analyses

Qualitative data were expressed as absolute numbers (percentages). Normally and non-normally distributed data were expressed as mean±standard deviation (SD) and median (interquartile range), respectively. Differences among groups were assessed by the Student *t* test and *Kruskal-Wallis* test, appropriately. *P* value <0.05 was significantly varied. Statistical analyses were performed using both GraphPad Prism (GraphPad, San Diego, CA) and SPSS (SPSS Inc., Chicago, IL) programs.

3. Results

3.1. Reproductive hormones levels, clinical characteristics and classification of BC in premenopausal women

As cases and controls were age-matched, there was no significant difference (*P*=0.156) in age. Also, there was no significant (*P* >0.05) difference in liver and kidney functions parameters, haemoglobin content (*P*=0.210), red (*P*=0.543) and white (*P*=0.134) blood cells and platelets counts (*P*=0.235) of BC patients compared with the controls (Table 1). Also, there was no significant difference in the serum level of FSH (*P*=0.486), LH (*P*=0.806), PRL (*P*=0.081) and PRG (*P*=0.474) hormones (Table 1). Some tumor features including tumor size, depth (stage), histological grade, lymph node invasion, and distant metastasis and expression of progesterone and estrogen receptors and HER2 protein were presented in Table 2.

Table 1. Clinical characteristics of premenopausal patients and controls

Variables	Breast cancer	Healthy	*P* value
Number	100	40	—
Mean age ±SD, years	37.6±7.4	36.5±6.9	0.156
Hemoglobin (g/dL)	11.5±2.15	12.5±1.85	0.210
RBCs ($\times10^{12}$/L)	4.4±0.92	4.4±0.53	0.543
WBCs ($\times10^{9}$/L)	7.9±1.8	8.05±1.91	0.134
Platelet count ($\times10^{9}$/L)	269.4±70.7	271.7±65.7	0.235
ALT (U/L)	23.5±4.2	21.6±6.1	0.529
AST(U/L)	28.14±6.14	25.12±8.11	0.517
Total bilirubin (mg/dL)	0.64±0.12	0.63±0.11	0.612
Albumin (g/dL)	3.92±0.39	4.0±0.32	0.522
Creatinine (mg/dL)	0.81±0.15	0.78±0.14	0.412
Urea (mg/dL)	26.1±5.34	23.5±4.7	0.611
CEA (U/L)	2.0 (1.0-5.0)	—	—
CA 15.3 (U/L)	12.0 (7.5-23.5)	—	—
FSH (µIU/mL)	13.2 (9.1-26)	15.1 (12.5-20.6)	0.895
LH (µIU/mL)	8.2 (4.1-13.2)	5.6 (3.9-9.8)	0.127
Prolactin (ng/mL)	7.02 (4.0-10.4)	6.8 (4.3-9.1)	0.525
Progesterone (ng/mL)	2.6 (1.07-8)	2.5 (1.5-7)	0.754

Normally and non-normally distributed data were expressed as mean± standard deviation (SD) and median (interquartile range), respectively. RBC: red blood cell; WBC: white blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CEA: carcinoembryonic antigen; CA15.3: cancer antigen 15.3; FSH: follicle-stimulating hormone; LH: luteinizing hormone.

Table 2. Classification of premenopausal breast cancer patients

Clinicopathological features	No. (%)
Primary tumor stage	
Early stage (T1–T2)	48 (48%)
Late stage (T3–T4)	52 (52%)
Lymph node invasion	
Negative (N0)	27 (27%)
Positive (N1)	73 (73%)
Metastasis	
Negative (M0)	87 (87%)
Positive (M1)	13 (13%)
Histological grade	
Low grade (G1–G2)	48 (48%)
High grade (G3)	52 (52%)
Tumor size	
Small (≤ 2 cm)	41 (41%)
Large (>2 cm)	59 (59%)
Estrogen receptor	
Negative	47 (47%)
Positive	53 (53%)
Progesterone receptor	
Negative	49 (49%)
Positive	51 (51%)
HER2	
Negative	55 (55%)
Positive	45 (45%)

3.2. Reproductive hormones and BC severity

In premenopausal BC patients, FSH (Table 3), LH (Table 4), PRL (Table 5) and PRG (Table 6) were not significantly (P >0.05) influenced as the disease progression including tumor late stages, lymph node invasion, distant metastasis, high grades, large size, negative progesterone and estrogen receptors and negative HER2 status.

Table 3. Impact of FSH levels on BC progression in premenopausal patients. Data were expressed as median (inter quartile range).

Categories	Number	FSH (µIU/mL)	*P* value
Primary tumor stage			
Early stage (T1-T2)	48	12.2 (9.1-30.1)	0.692
Late stage (T3-T4)	52	14.85 (7.23-26.5)	
Lymph node invasion			
Negative (N0)	27	13.95 (3.91-24.28)	0.841
Present (N1)	73	13.45 (10.15-29.28)	
Metastasis			
Negative (M0)	87	12.99 (9.1-24.5)	0.237
Present (M1)	13	19.2 (11.36-42.62)	
Tumor histological grade			
Low grade (G1-G2)	48	18.1 (9.5-35.0)	0.199
High grade (G3)	52	13.1 (6.1-16.0)	
Tumor size			
Small (≤ 2 cm)	41	12.1 (6.7-16.6)	0.136
Large (>2 cm)	59	15.0 (10.4-30.3)	
Progesterone receptor			
Negative	47	14.9 (11.28-26.0)	0.327
Positive	53	11.54 (6.0-30.1)	
Estrogen receptor			
Negative	49	14.9 (11.2-27.5)	0.362
Positive	51	11.53 (5.9-30.1)	
HER2			
Negative	55	15.45 (7.28-32.17)	0.171
Positive	45	11.72 (9.11-19.3)	

Table 4. Impact of LH levels on BC progression in premenopausal patients. Data were expressed as median (inter quartile range).

Categories	Number	LH (μIU/mL)	*P* value
Primary tumor stage			
Early stage (T1-T2)	48	8.4 (4.1-14.7)	0.738
Late stage (T3-T4)	52	8.0 (4.2-13.2)	
Lymph node invasion			
Negative (N0)	27	6.4 (3.9-12.6)	0.258
Present (N1)	73	8.8 (4.3-13.4)	
Metastasis			
Negative (M0)	87	7.8 (4.1-12.5)	0.519
Present (M1)	13	8.4 (4.1-28.9)	
Tumor histological grade			
Low grade (G1-G2)	48	8.6 (4.7-23.6)	0.335
High grade (G3)	52	7.4 (4.0-11.4)	
Tumor size			
Small (≤ 2 cm)	41	5.1 (3.9-11.7)	0.102
Large (>2 cm)	59	9.0 (4.9-20.6)	
Progesterone receptor			
Negative	47	9.5 (6.4-17.1)	0.012
Positive	53	4.7 (2.7-12.6)	
Estrogen receptor			
Negative	49	9.8 (6.3-15.9)	0.033
Positive	51	5.0 (3.1-12.5)	
HER2			
Negative	55	6.4 (4.0-18.5)	0.606
Positive	45	8.8 (4.7-12.4)	

Table 5. Impact of prolactin levels on BC progression in premenopausal patients. Data were expressed as median (inter quartile range).

Categories	Number	Prolactin (ng/mL)	*P* value
Primary tumor stage			
Early stage (T1-T2)	48	5.9 (3.4-10.2)	0.102
Late stage (T3-T4)	52	9.2 (5.3-10.5)	
Lymph node invasion			
Negative (N0)	27	6.6 (3.5-10.0)	0.492
Present (N1)	73	7.4 (3.9-10.5)	
Metastasis			
Negative (M0)	87	7.0 (3.9-10.4)	0.952
Present (M1)	13	6.9 (2.7-10.5)	
Tumor histological grade			
Low grade (G1-G2)	48	5.9 (3.3-10.3)	0.159
High grade (G3)	52	8.9 (5.1-10.7)	
Tumor size			
Small (≤ 2 cm)	41	7.5 (5.3-10.4)	0.653
Large (>2 cm)	59	6.5 (3.5-10.5)	
Progesterone receptor			
Negative	47	9.1 (5.3-10.9)	0.057
Positive	53	6.1 (2.8-10.1)	
Estrogen receptor			
Negative	49	8.2 (4.9-10.3)	0.445
Positive	51	6.4 (3.2-10.4)	
HER2			
Negative	55	9.2 (4.1-10.4)	0.291
Positive	45	6.1 (3.6-10.3)	

Table 6. Impact of progesterone levels on BC progression in premenopausal patients. Data were expressed as median (inter quartile range).

Categories	Number	Progesterone (ng/mL)	*P* value
Primary tumor stage			
Early stage (T1-T2)	48	2.9 (1.4-9.1)	0.529
Late stage (T3-T4)	52	2.9 (0.98-7.01)	
Lymph node invasion			
Negative (N0)	27	1.2 (0.93-6.7)	0.174
Present (N1)	73	3.5 (1.5-9.1)	
Metastasis			
Negative (M0)	87	2.6 (1.2-8.6)	0.914
Present (M1)	13	3.5 (0.63-10.5)	
Tumor histological grade			
Low grade (G1-G2)	48	2.8 (1.3-8.9)	0.901
High grade (G3)	52	3.0 (0.99-8.1)	
Tumor size			
Small (≤ 2 cm)	41	3.1 (1.2-9.9)	0.570
Large (>2 cm)	59	2.7 (0.99-6.6)	
Progesterone receptor			
Negative	47	3.6 (1.4-10.4)	0.148
Positive	53	2.1 (0.96-5.2)	
Estrogen receptor			
Negative	49	3.6 (1.7-10.5)	0.091
Positive	51	2.1 (0.94-5.7)	
HER2			
Negative	55	2.0 (0.95-4.5)	0.094
Positive	45	4.2 (1.8-9.7)	

4. Discussion

Usually, females <40 years have a more unfavorable prognosis owing to a more aggressive BCs compared to older cases **(Badawy *et al.,* 2009)**. Despite advances in treatment, diagnosis, and screening, about one-fifth of affected females will die **(Janssens *et al.,* 2007)**. In BC treatment, chemotherapy is fundamental; however, antineoplastic agents may results in toxic adverse and severe effects **(Anand *et al.,* 2023)**. BCs generally respond to initial chemotherapy, but acquired or intrinsic multidrug resistance may restrict BC therapy **(Tufail *et al.,* 2022)**. In BC cases, about 90% of deaths were related to the metastases growth and development at distant sites **(Tungsukruthai *et al.,* 2018)**. It is, therefore, vital to evaluate risk factors associated with BC severity to improve or

prevent the disease prognosis particularly in premenopausal women.

Several reproductive factors are related to BC risk, potentially through a hormonal pathway. Reproductive hormones are essential in lactation and mammary development and may be an association between risk factors and BC **(Eliassen *et al.*, 2007)**. The aim of this study is to evaluate FSH, LH, PRL and PRG reproductive hormones profile in premenopausal BC patients comparing to age-matched healthy women and to assess the association between their circulating levels with BC severity including advanced stages, high histological grade, large tumor size, lymph node invasion, distant metastasis and negative expression of progesterone and estrogen receptors and HER2 protein.

In this study, there was no significant (P>0.05) difference in the serum levels of FSH, LH, PRL and PRG hormones between BC cases and healthy controls. Also these hormones were not significantly (P >0.05) influenced the disease progression including tumor late stages, lymph node invasion, distant metastasis, high grades, large size, negative progesterone and estrogen receptors and negative HER2 status.

In accordance with the obtained results, future studies may support the main result of this study that FSH, LH, PRL and PRG hormones did not affect both BC development and progression or aggressiveness behavior. In both early and advanced BC patients (before and after mastectomy), **(Wang *et al.*, 1976)** found that the mean plasma LH and FSH in females with early BC are the same as in normal controls Also regarding mastectomy, there was no associated changes in these hormones level.s. Moreover in cases with advanced BC, the mean FSH and LH levels did not significantly differed from that of normal subjects **(Wang *et al.*, 1976)**. **(Zhou *et al.*, 2013)** reported that there was no significant correlation between the PRL, PRG, LH and FSH hormone levels, and BC lymphovascular invasion and BC tumor stages. Among premenopausal BC patients, **(Eliassen *et al.*, 2007)** found that benign breast disease, lactation duration and age at menarche were not related to PRL levels. Conversely, they found that only family history of BC in part was related to significantly increased PRL levels compared to no family history (15.9 *vs.* 14.3 ng/mL) but the level of significant was low (P=0.04). In most BC cell lines, other data found that LH receptors expression is very low (undetectable) indicating a limited role for LH signaling in BC tissue **(Cooley *et al.*, 2012)**. In the same line, Boukaidi et al. reported, in either normal or malignant mammary

epithelial cell lines, that such infertility hormones related regimens (LH, FSH, and human chorionic gonadotropin (HCG)) do not show an increase in colony growth or cell proliferation. They suggested that the potential transformation risk of mammary cell may be related to these hormones may be associated with indirect endocrine effects on breast cell physiology **(Boukaidi *et al.*, 2012)**.

5. Conclusion

This study point out that reproductive hormones including FSH, LH, PRL and PRG are not related to BC development or progression risks. Despite our important result, some limitations including retrospective nature and single-center cohort may exist. Thus, further multicenter studies including additional cohort are required to validate these observations.

Conflict of interest None

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6. References

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الأرتباط بين بعض هرمونات التكاثر وتقدم ورم سرطان الثدى في السيدات قبل سن اليأس

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ينمو وينتشر سرطان الثدي في بيئة غنية بالهرمونات مما يؤثر سريريا على هذا المرض وعلى خصائصه البيولوجية. في النساء قبل انقطاع الطمث (الصغار بالسن)، يتم إكتشاف سرطان الثدي في مراحل متقدمة و متأخرة وقد يكون هذا نتيجة لعدم تركيز برامج الفحص والكشف المبكر على النساء الشابات. هدفت هذه الدراسة إلى تقييم العلاقة بين الهرمونات المتعلقة بالتكاثر (مثل هرمون تحفيز الجريبات (FSH)، وهرمون الملوتن (LH)، والبرولاكتين (PRL) والبروجيستيرون (PRG)) وتطور وتدهور سرطان الثدي. تم قياس مستويات الهرمونات في مصل الدم في 100 مريضة بسرطان الثدي قبل انقطاع الطمث و40 امرأة سليمة من نفس العمر. كشفت النتائج أنه لم يكن هناك فرق كبير في مستوى هذه الهرمونات بين حالات سرطان الثدي والنساء الأصحاء. علاوة على ذلك، في مريضات سرطان الثدي قبل انقطاع الطمث، لم تؤثر هذه الهرمونات التناسلية بشكل كبير ($P>0.05$) على تطور المرض بما في ذلك المراحل المتأخرة من الورم، وغزو العقد الليمفاوية، وإنتشار المرض إلى الأعضاء البعيدة، والدرجات العالية، والحجم الكبير من الورم وكذلك مستقبلات البروجسترون والإستروجين السلبية وحالة HER2 السلبية. في النهاية، يبدو أن مستويات هذه الهرمونات (FSH وLH وPRG وPRL) في الدم لا ترتبط بتطور سرطان الثدي و/أو تقدمه. ويعتبر هذا إضافة مهمة لعلاج العقم عند النساء قبل انقطاع الطمث