# Pregnancy Associated Breast Cancer Prognosis and Outcome, Qatar Experience

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## Abstract

**Background:** During pregnancy, breast cancer is the most diagnosed cancer. Personal and social factors tailored to the patient should be taken into account when deciding about the best treatment plan, hence, the application of precision medicine in this era is required. The impact of many risk factors on Pregnancy Associated Breast Cancer (PABC) prognosis is incompletely understood. Our study aims to assess the prevalence of PABC in Qatar and to study the association between the individual risk factors and the disease, pregnancy, fetal and maternal outcome.

**Methods:** This is a retrospective data review for all women seen at breast surgery, Oncology and women's hospital in Hamad Medical Corporation, Qatar, who were diagnosed with Breast cancer during pregnancy and post-partum period up to one year after delivery during the period in 01/01/2011 to 31/12/2019.

**Results:** The prevalence of PABC was about 32 in 1,000 among women diagnosed with breast cancer. Most patients were young at diagnosis. The mean age of menarche was 13 years. Family history of breast/ovarian cancer and parity of ≥ 3 had the higher association to PABC (21%, 57% respectively). The most common histological type of PABC was Invasive ductal carcinoma (92%) with large size tumors of >2 cm (n=43). Lymph node involvement was apparent in 75% of the cases. Most tumors were hormone receptor positive (68%) and HER2 negative (68%). 30% of the tumors were luminal B subtype. BRCA1 mutation was more evident in PABC patients than BRCA2 (17% compared to 0%).

Most pregnant ladies had full term delivery (45%) of healthy babies (74%) with average weight of 3 kg. Only 11% of the patients had termination of pregnancy. The median overall survival was 88 months. None of the risk factors were correlated to pregnancy outcome. Factors associated with good fetal outcome were; diagnosis at ≥ 12 weeks gestational age and parity ≥ 3. Factors correlated to poor survival were; parity ≥ 3, lymph node involvement, presence of LVI and high ki67 ≥ 20%.

**Conclusion:** These findings confirm the importance of incorporating the patient & tumor characteristics and related risk factors in designing individualized management plan for patients with PABC.

**Keywords:** Pregnancy associated breast cancer; Risk factors; Clinical outcome

## Abbreviations

PABC: Pregnancy Associated Breast Cancer; MDT: Multidisciplinary Team; NCCCR: National Cancer Center for Research; HGH: Hamad General Hospital; Her2n: Human Epidermal growth factor Receptor 2-neu; Ki-67: Protein Encoded by the MKI67 Gene; LVI: Lympho-Vascular Invasion; WWRC: Women's Wellness and Research Center; BC: Breast Cancer; IUGR: Intrauterine Growth Retardation; IUFD: Intrauterine Fetal Death

## Introduction

The second cause of death among middle aged women is cancer [1]. This is linked to the observation that the occurrence of cancer around pregnancy is not uncommon, it affects between 1/1,000 and 1/6,000 pregnant women [1]. During pregnancy, breast cancer is one of the most diagnosed cancer [1,2] and the most common cancer in Qatar is breast cancer. The prevalent age group is 40 to 50 years old [3]. The median age at diagnosis is about 48 years, and about two-thirds of women with breast cancer are younger than 50 years. One of the considerations of early age group breast cancer is correlated with BRCA gene mutation in Arabic population. In 2017, Kim et al. [4] linked the adverse tumor characteristics noticed in PABC to the poor prognosis observed with this

type of tumors.

As more women start childbearing after age of 30, it is expected that more cases of breast cancer during pregnancy will be diagnosed [1,2,5]. Despite breast clinical examination, delay in diagnosis with nodal involvement is noticed in about 70% of cases [1]. The diagnosis of breast cancer around pregnancy carries many worries both for the patient and for the medical team; termination of pregnancy is not generally used as it does not lead to a better prognosis [1]. Chemotherapy is contraindicated during the first trimester [1]. Loibl et al. [2] concluded that surgery can be used as it is relatively safe in pregnancy. During the 2nd and 3rd trimesters of pregnancy, Anthracycline-based chemotherapy is a safe option. Hormonal therapy and Radiotherapy can't be used till after delivery [1,2,6-8]. Due to the limited data available, the use of systemic treatment such as tamoxifen, taxanes and trastuzumab is not recommended. Hence, delay in the treatment is often seen.

In all cases, a multidisciplinary meeting among obstetricians, gynecologists, surgical oncologists, radiation oncologists and medical oncologists is needed to reach to the optimal way to treat these patients. For the medical team; personal, medical, religious and social factors should be considered when deciding about the treatment plan. Moreover, the lack of large randomized trials and cohort studies in this era in the medical literature makes it more difficult for the clinicians to decide about the best plan of care.

Despite the increasing number of cases diagnosed with pregnancy-associated breast cancer [9,10], it is still under studied, especially in the Middle East region. The impact of many factors on PABC prognosis, such as: Age at diagnosis, tumor characteristics and BRCA gene mutations, is incompletely understood.

Our study aims to assess the prevalence of PABC in Qatar and to study the association between the proposed risk factors and the disease, pregnancy and fetal outcome.

This is a retrospective data review of all women referred to breast MDT, Medical Oncology in NCCCR and breast clinic in HGH in Qatar who are diagnosed with breast cancer during pregnancy and up to one year after delivery or during lactation.

This study will help optimize breast cancer care and management in PABC cases and developed data base for future research in these population.

## Methodology

### Objectives

The primary objective is to collect data on the prevalence of pregnancy associated breast cancer in Qatari population. And to assess prognosis and clinical outcomes for the patients, the fetus and the pregnancy.

Our secondary objective is to determine the risk factors associated with PABC outcome, for example: Age at diagnosis, stage at diagnosis, histopathological feature {Hormone receptors status, HER2neu, LVI, Grade of the disease, ki67} and BRCA gene results.

This is a retrospective data review of all women referred to breast MDT, Medical Oncology in National Cancer Center for Research and Breast Surgery Clinic in Hamad General Hospital in Qatar, who were diagnosed with breast cancer during pregnancy and up to one year after delivery or during lactation, in order to evaluate prevalence, related risk factors, prognosis and outcome of those patients, the

pregnancy and the fetus.

We collected data available from 01/01/2011 to 31/12/2019. Breast cancer cases diagnosed after being seen in the breast surgery clinic in HMC, breast MDT and breast cancer medical oncology clinics NCCCR. Pregnant and lactation cases were diagnosed after being evaluated in Women's Wellness and Research Center (WWRC).

We collected data on patient demographics and history: Nationality, age at diagnosis, date of diagnosis, gestational age at diagnosis, duration of lactation/post-partum period at diagnosis, parity, related risk factors (family history of cancer, age of menarche, prior use of hormones) and prior breast feeding. Tumor characteristics (location, phenotype, grade, stage, tumor markers) were analyzed in addition to result of BRCA gene test. For the patient, we studied treatment received (including termination) and survival data. We also looked at pregnancy outcome (miscarriage, IUGR, IUFD, pre-term delivery or full-term delivery) and fetal outcome (alive, alive with complications, birth weight, still birth).

All data were collected from the HMC patient medical records

### The definition of pregnancy-associated breast cancer

PABC is defined as BC occurring during gestation and/or within one year after childbirth.

### Statistical analysis

Descriptive statistics were used to summarize patient's demographic, epidemiological, clinical and laboratory characteristics. Frequencies and proportions were described for categorical variables, while median and range were performed for the continuous variables with normal distribution.

Intergroup difference was compared using the t test or Wilcoxon signed-rank test for continuous variables nonparametric variables, and the $\chi^2$ test or Fisher exact test for categorical variables (e.g., gender), as appropriate. The impact of age, Gestational age at diagnosis, parity, family history, tumor grade, tumor size, number of positive LN, molecular subtype of the tumor, presence of LVI, ki67% and the presence/absence of BRCA ½ that influence survival was evaluated in the regression analysis. Correlation between variables was examined using Spearman and Pearson correlation coefficients. They looked at the correlation between risk factors and mortality.

Survival analyses were plotted by using the Kaplan-Meier method to determine the cumulative survival probability, and overall survival time was calculated from the time of diagnosis to the date of death from any cause or the date at which the pregnant women with breast cancer t was last known alive. Statistical significance is indicated by p-value of 0.05 or less. STATA version 12.0 (Statacorp, College Station, TX, USA) has been used for exploratory data analysis and descriptive statistics.

## Results

A total of 53 women were included in this retrospective study whom were pregnant or lactating (up to 1 year after delivery) at the time of breast cancer diagnosis.

### Prevalence of pregnancy associated breast cancer

The total number of breast cancer cases diagnosed during the study period (2011-2019) is 1,503 and the total number of PABC diagnosed during the study period is 53.

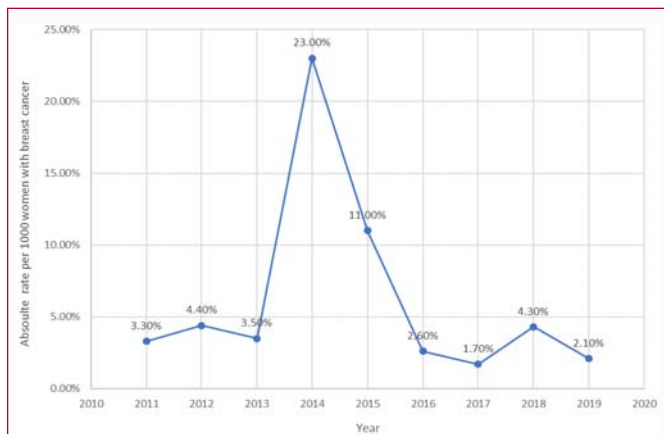The prevalence of pregnancy-associated breast cancer is about 32

**Figure 1:** The prevalence of pregnancy-associated breast cancer among women diagnosed with breast cancer in Qatar 2011-2019.

**Table 1:** Characteristics of patients diagnosed with pregnancy associated breast cancer.

| Variables | Values | |
|---|---|---|
| **Age of Diagnosis** | | |
| <40 yrs | 39 | 74% |
| ≥ 40yrs | 14 | 26% |
| Median/Range, yrs | 36 (25-45) | |
| **Gestational Age at Diagnosis** | | |
| <12 weeks | 11 | 37% |
| ≥ 12 weeks | 19 | 63% |
| **Parity** | | |
| 0 | 6 | 11% |
| 1 | 7 | 13% |
| 2 | 10 | 19% |
| ≥ 3 | 30 | 57% |
| **Risk Factors** | | |
| F/H(Yes) | 11 | 21% |
| Oral Contraceptive Pills (Yes) | 2 | 4% |
| Clomide 9 (Yes) | 1 | 2% |
| IVF (Yes) | 0 | 0% |
| Breast Feeding (Yes) | 9 | 17% |
| Age Of Menarche (Mean ± SD), yrs | 13.2 ± 1.39 | |

in 1,000 among women diagnosed with breast cancer, ranged from 21 to 77 cases in 1,000 among women diagnosed with breast cancer (Figure 1).

### Patient characteristics

Our analysis showed that 39 patients (74%) were diagnosed below age 40 years. Most of the women in our cohort were Para 3 or more at the time of diagnosis (57%) and 63% were diagnosed at 12 weeks gestational age or later (Figure 2). Of the risk factors, family history of breast and/or ovarian cancer has the higher association to the diagnosis of PABC (21%) (Figure 3). The mean age of menarche among the study participants was 13 (Table 1).

### Tumor characteristics

Review of the tumor characteristics of PABC in our cohort showed that Invasive ductal carcinoma is the most frequently occurring
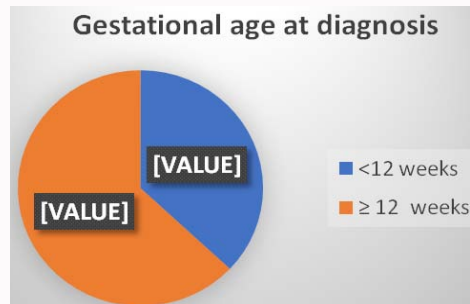


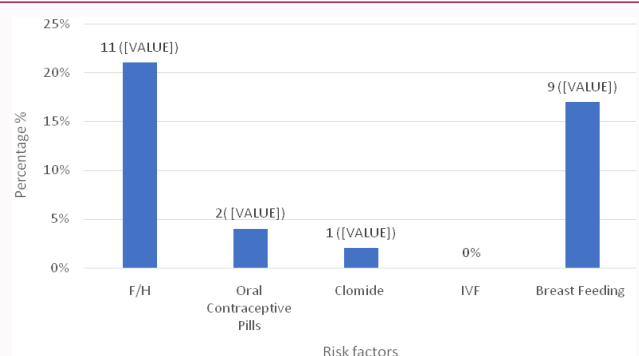**Figure 2:** Gestational age at breast cancer diagnosis for pregnant women diagnosed with breast cancer.



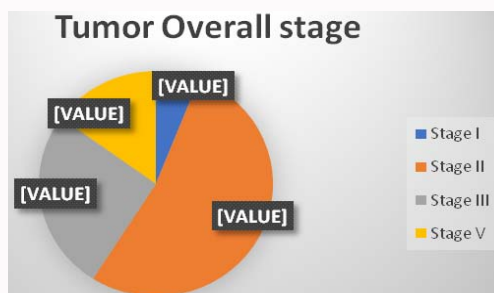**Figure 3:** Risk factors related to diagnosis of pregnancy associated breast cancer.



**Figure 4:** Overall tumor stage for patients diagnosed with pregnancy associated breast cancer.

histological type observed in 92% of cases. Most of the tumors are grade 2 (66%). Eight one percent of the tumors are large (more than 2 cm in size). Lymph node involvement is seen in 38 patients (75%) and only eight patients had metastases at the time of breast cancer diagnosis. Most of the tumors are stage II at diagnosis (53%) (Figure 4 and Table 2).

Tumors are found to be hormone receptor positive in 68% of cases and HER2 positive in 32%. The most common molecular subtype is luminal B subtype [with HR +ve & HER2 -ve expression & Ki67 of 20% or more] breast cancer observed in 30% of the patients.

Gene expression patterns for PABC in this analysis showed that 17% of the cases have BRCA1 mutation compared to none with BRCA2 mutation (Figure 5).

### Pregnancy, fetal and maternal outcome

We found that 45% of pregnant women with breast cancer diagnosis had full term delivery (Figure 6). Seventy four percent of the ladies delivered a live healthy baby. The average birth weight was
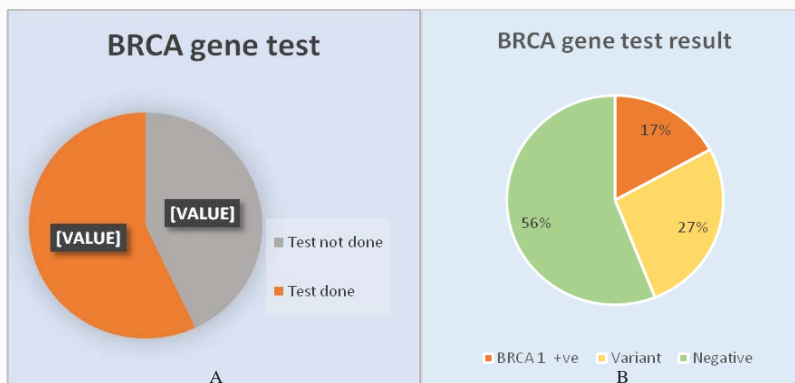
**Figure 5:** BRCA gene test for patients diagnosed with pregnancy associated breast cancer. (A) BRCA gene test doe/not done for patients. (B) BRCA gene test result for patients who had the test done.

**Table 2:** Tumor characteristics of patients diagnosed with pregnancy associated breast cancer.

| Tumor Phenotype | | |
|---|---|---|
| Invasive Ductal Carcinoma (IDC) | 49 | 92% |
| Ductal Carcinoma *In Situ* (DCIS) | 0 | 0% |
| Invasive Lobular Carcinoma (ILC) | 1 | 2% |
| Lobular Carcinoma *In Situ* (LCIS) | 0 | 0% |
| Others | 3 | 6% |
| **Tumor Grade** | | |
| 1 | 1 | 2% |
| 2 | 35 | 66% |
| 3 | 20 | 38% |
| **Tumor Size T** | | |
| T1 (≥ 2 cm) | 9 | 17% |
| T2,3,4 (>2 cm) | 43 | 81% |
| **lymph node involvement (N)** | | |
| N0 (no LN involvement) | 13 | 25% |
| N 1,2,3 (with LN involvement) | 38 | 75% |
| **Metastases (M)** | | |
| M0 (no metastases) | 45 | 85% |
| M1 (with metastases) | 8 | 15% |
| **Tumor overall stage** | | |
| Stage I | 3 | 6% |
| Stage II | 28 | 53% |
| Stage III | 14 | 26% |
| Stage V | 8 | 15% |
| **Hormone receptors** | | |
| Negative | 17 | 32% |
| Positive | 36 | 68% |
| **HER-2** | | |
| Negative | 36 | 68% |
| Positive | 17 | 32% |
| **ki67** | | |
| ≤ 20% | 17 | 32% |
| >20% | 29 | 55% |
| N/A | 7 | 13% |

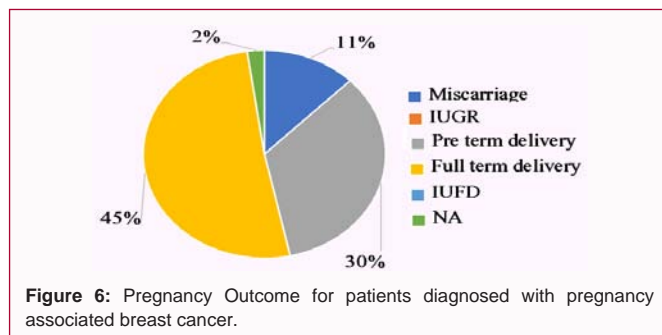| LVI | | |
|---|---|---|
| Negative | 17 | 32% |
| Positive | 15 | 28% |
| N/A | 21 | 40% |
| **BC molecular subtype** | | |
| (luminal A) HR +ve, her -ve, ki67<20% | 7 | 13% |
| (luminal B)HR +ve, her -ve, ki67 ≥ 20% | 16 | 30% |
| (HER 2 over expression) HR -ve, HER2 +ve | 5 | 9% |
| HR +ve HER2 +ve | 12 | 23% |
| (triple negative ) ER -ve, PR -ve, Her2 -ve | 11 | 21% |
| Luminal type Ki67 not known | 2 | 4% |



**Figure 6:** Pregnancy Outcome for patients diagnosed with pregnancy associated breast cancer.



**Figure 7:** The median follow-up and the median overall survival for patients diagnosed with pregnancy associated breast cancer.

3 kg. At latest clinical follow up, 43 patients were alive (81%). The Median follow up is 25 months and the median overall survival is 88 months (Figure 7). Most of the patients didn't have termination of the pregnancy (89%), all patients who had termination of their pregnancy was before 12 weeks gestational age (Table 3).

**Table 3:** Pregnancy, fetal and maternal outcome for patients diagnosed with pregnancy associated breast cancer.

| Pregnancy out come | | |
|---|---|---|
| Miscarriage | 6 | 11% |
| IUGR | 0 | 0% |
| Pre term delivery | 16 | 30% |
| Full term delivery | 24 | 45% |
| IUFD | 0 | 0% |
| NA | 1 | 2% |
| **Fetal out come** | | |
| Birth weight | 3 (1.3-4.5) | |
| Alive | 39 | 74% |
| A live with complications | 1 | 2% |
| **Maternal come** | | |
| A live | 43 | 81% |
| Dead | 10 | 19% |
| **Termination of Pregnancy** | | |
| Yes | 6 | 11% |
| No | 47 | 89% |

**Table 4:** Risk factors correlated with pregnancy outcome in patients diagnosed with pregnancy associated breast cancer.

| Variables | Pregnancy outcome | | |
|---|---|---|---|
| | None full term (miscarriage, IUGR, pre term, IUFD) n=24 | Full term n=29 | P-value |
| **Age of Diagnosis** | | | |
| <40 yrs | 20 (51%) | 19 (48%) | 0.14 |
| ≥ 40 yrs | 4 (29%) | 10 (71%) | |
| **Gestational Age at Diagnosis** | | | |
| <12 weeks | 2 (15%) | 11(85%) | 0.18 |
| ≥ 12 weeks | 7 (37%) | 12 (63%) | |
| **Parity** | | | |
| <3 | 11 (48%) | 12 52%) | 0.74 |
| ≥ 3 | 13 (43%) | 17 (57%) | |
| **F/H** | | | |
| Yes | 3 (33%) | 6 (67%) | 0.42 |
| No | 21 (48%) | 23 (52%) | |
| **Breast Feeding** | | | |
| Yes | 8 (42%) | 11(58%) | 0.83 |
| No | 1 (50%) | 1 (50%) | |
| **Hormonal Use ( OCP, induction, IVF)** | | | |
| Yes | 2 (67%) | 1 (33%) | 0.46 |
| No | 22 (45%) | 27 (55%) | |

## Risk factors correlated with pregnancy outcome

We looked at age at the time of diagnosis, gestational age at the time of diagnosis, parity, FH of breast/ovarian cancer, history of breast feeding and history of hormonal use; none of those risk factors is found to be correlated to pregnancy outcome with significant P value (Table 4).

The trend observed is that: Age of 40 or more at the time of

**Table 5:** Risk factors correlated with fetal outcome in patients diagnosed with pregnancy associated breast cancer.

| Variables | Fetal outcome | | P-value |
|---|---|---|---|
| | Alive | A live with complications/ still birth | |
| **Age** | | | |
| <40 yrs | 30 (73%) | 11 (27%) | 0.782271843 |
| ≥ 40 yrs | 9 (69%) | 4 (31%) | |
| **GA** | | | |
| <12 weeks | 5 (33%) | 10 (67%) | 0.000670852 |
| ≥ 12 weeks | 17 (89%) | 2 (11%) | |
| **Parity** | | | |
| <3 | 16 (59%) | 11 (41%) | 0.033440639 |
| ≥ 3 | 23 (85%) | 4 (15%) | |
| **F/H** | | | |
| Yes | 5 (56%) | 4 (44%) | 0.178155196 |
| No | 34 (77%) | 10 (23%) | |
| **Breast Feeding** | | | |
| Yes | 9 | 0 | The Fisher exact test statistic value is 1. |
| No | 11 | 0 | The result is not significant at p<0.05. |
| **Hormonal Use** | | | |
| Yes | 2 | 0 | The Fisher exact test statistic value is 1. |
| No | 37 | 0 | The result is not significant at p<0.05. |

diagnosis & diagnosis at 12 weeks GA or earlier is linked to good pregnancy outcome.

## Risk factors correlated with fetal outcome

Our analysis showed that factors associated with good fetal outcome are; ≥ 12 weeks gestational age at the time of diagnosis and parity of ≥ 3 at diagnosis. Eight nine percent of patients who were diagnosed at 12 weeks gestation or later had alive healthy babies compared to 33% for patients who were diagnosed before 12 weeks gestation (P=0.0006) and 85% of patients with high parity has alive healthy babies compared to 59% for patients with parity <3 (P=0.033) (Table 5).

## Risk factors correlated with maternal outcome and survival

Multivariate logistic regression of our data showed that high parity of 3 or more at the time of breast cancer diagnosis, lymph node involvement, and presence of LVI and high ki67 of 20% or more are correlated with lower survivals (OR=54.08 - P=0.03, OR=9.9 - P=0.05-, OR=16.6 - P=0.05, OR=18.3 - P=0.04 respectively) (Table 6).

## Discussion

This project is the first nationwide review of women with PABC in the state of Qatar. We included all patients with breast cancer diagnosed during pregnancy and/or lactation or during the 12 months following delivery treated at Hamad Medical Corporation in the state of Qatar between 2011 and 2019. The following elements were analyzed: Patient demographics, clinic- pathological features of the disease, risk factors related to PABC, presence of BRCA gene mutation, pregnancy, fetal & maternal outcomes and the survival rate.

We were able to re-demonstrate the previous finding of

**Table 6:** Risk factors correlated with maternal outcome and survival in patients diagnosed with pregnancy associated breast cancer.

| Variables | OR | P-value | 95% CI |
|---|---|---|---|
| **Age** | | | |
| <40 yrs | | 1 | |
| <40 yrs | 0.11 | 0.34 | (0.01, 2.96) |
| **Gestational Age at Diagnosis** | | | |
| <12 weeks | | 1 | |
| ≥ 12 weeks | 0.69 | 0.81 | (0.3, 3.01) |
| **Parity** | | | |
| <3 | | 1 | |
| ≥ 3 | 54.1 | 0.03 | (29.86, 96.53) |
| **F/H** | | | |
| Yes | | 1 | |
| No | 0.31 | 0.57 | (1.49, 10.73) |
| **Tumor Grade** | | | |
| <2 | | 1 | |
| ≥ 2 | 0.09 | 0.28 | (0.01, 2.28) |
| **Tumor stage** | | | |
| <II | | 1 | |
| ≥ II | 0.84 | 0.88 | (0.16, 5.09) |
| **no-of positive LN** | | | |
| <N1 | | 1 | |
| ≥ N1 | 9.9 | ≈ 0.05 | (3.16, 28.05) |
| **Molecular subtype** | | | |
| Others | | 1 | |
| Triple negative | 1.54 | 0.8 | (0.54, 9.58) |
| **LVI** | | | |
| -ve | | 1 | |
| +ve | 16.5 | 0.05 | (6.76, 91.44) |
| **Ki67** | | | |
| <20% | | 1 | |
| ≥ 20% | 18.1 | 0.04 | (8.49, 87.55) |
| **BRCA 1 /2** | | | |
| Yes | | 1 | |
| No | 1.58 | 0.72 | (0.49, 8.06) |

Asgeirsson et al. [11] concluding that the prevalence of PABC in 3.2%. Most of our patients were young (<40 years old). We found that family history of breast/ovarian cancer and high parity at the time of diagnosis are frequently observed in PABC among all risk factors which are consistent with the finding by Ningqi et al. [12]. Early age of menarche (13 years) was noticed in PABC patients [4,13].

Our current analysis showed that the most common histological type of breast cancer during pregnancy is Invasive ductal carcinoma confirming the previous finding by Polivka et al. [14]. Large size tumors (>2 cm) were noticed in high percentage of PABC population as shown by Langer et al. [15]. Moreover, most patients had lymph node involvement at the time of diagnosis as previously observed by Halaska et al. [16]. We found that BRCA1 mutation was more evident in PABC patients than BRCA2 which confirms the previous findings of Rouzier et al. [1]. In contrary to previous studies, this review showed that most tumors are hormone receptor positive and HER2 negative. This is a new finding which might be related to tumor characteristics in the Middle East, however, this need to be further evaluated in a larger sample size. Our study showed that the most common breast cancer molecular subtype in pregnant women is luminal B (HR positive, HER2 negative, Ki67 ≥ 20%).

Our data showed that most pregnant ladies with breast cancer had full term delivery of healthy babies with average weight of 3 kg as shown by Halaska et al. [16]. Few patients had termination of pregnancy as a consequence of their diagnosis as observed by Rouzier et al. [1]. In our cohort, we have superior overall survival (7.3 years) compared to previous study by Ali et al. [17] (4.9 years). This difference might be attributed to the higher percentage of positive hormone receptor cases in our cohort and to the advances of local and systemic therapy.

As per our data, none of the risk factors examined were correlated to pregnancy outcome. Factors found to be associated with good fetal outcome are; diagnosis at ≥ 12 weeks gestational age and high parity (of 3 or more) at the time of breast cancer diagnosis. Our analysis showed that, of the patient characteristics, high parity of 3 or more is associated with bad maternal outcome. Of the tumor characteristics, factors correlated to poor survival are; lymph node involvement, presence of LVI and high ki67 ≥ 20% as previously reported by Cianfrocca et al. [18]. Triple negative & HER2 enriched tumors were less representative in our cohort because most of the tumors were hormone receptor positive.

# Conclusion

The assessment and management of women with PABC requires a multidisciplinary approach. The treatment of this unique group of breast carcinoma patients' needs to be carefully planned with consideration of factors related to fetal, pregnancy and maternal outcome.

As the objective is to cure the mother and to deliver a healthy baby simultaneously, through discussion with the patients about risk & benefit of all therapeutic options is a key to best individualized patient care and outcome.

Further research in the era of breast cancer during pregnancy/ lactation will help to identify other risk factors for PABC and its relation to the outcome which will help to formulate the best plan of care for the patient and the baby. Through the application of precision medicine, such studies could contribute to improving survival by incorporating those risk factors in the treatment recommendation on individual bases.

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