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PREGNANCY AFTER BREAST CANCER: OBSTETRICS AND FETO-MATERNAL OUTCOMES

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ABSTRACT – *Objective:* Pregnancy after breast cancer (BC) is possible and does not have a negative impact on prognosis, even in hormone receptor-positive or *BRCA1/2*-mutated patients. Despite this, the estimated pregnancy achievability in BC survivors is significantly inferior when compared to that of women who did not have cancer.

Materials and Methods: This study investigated pregnancies after BC in 18 women monitored at the Oncofertility Center of the Italian Sandro Pertini Hospital. We compared maternal, fetal, and neonatal outcomes against general population data. Then, we evaluated the impact of chemotherapy on feto-maternal outcomes.

Results: Compared to findings from the general population, our results show that pregnancy after BC may have more obstetrical complications, such as premature delivery and cesarean section; in addition, our research showed a possible correlation between the occurrence of gestational diabetes and previous chemotherapy treatment. The rate of breastfed survivors appeared lower than that of women in the general population, as summarized in the article's main findings.

Conclusions: Based on our data, pregnancy after BC is safe for both mother and fetus/newborn but requires strict follow-up in referral centers to best manage possible obstetric complications, particularly in women who have undergone chemotherapy.

KEYWORDS: Breast cancer, Oncofertility, IVF, Reproductive hormones, Pregnancy, Obstetrical complications, Breastfeeding.

INTRODUCTION

Breast cancer (BC) is the most common malignancy in women worldwide, with about 2.1 million newly diagnosed cases in 2018 and 2.3 million in 2020[1,2]. Approximately 13% of women develop invasive BC over their lifetime, with 5-7% of cases occurring in patients under 40 years[3]. Thanks to improvements in oncological treatments, patients with previous breast cancer are the largest group of young-onset cancer survivors[4]. Many young breast cancer patients are candidates for chemotherapy and can suffer from its potential negative impact on quality of life and family planning due to short-term and long-term side effects. Gonadotoxicity is one of the main side effects of anticancer therapies, especially of chemotherapy, leading to premature ovarian insufficiency (POI) and relat-

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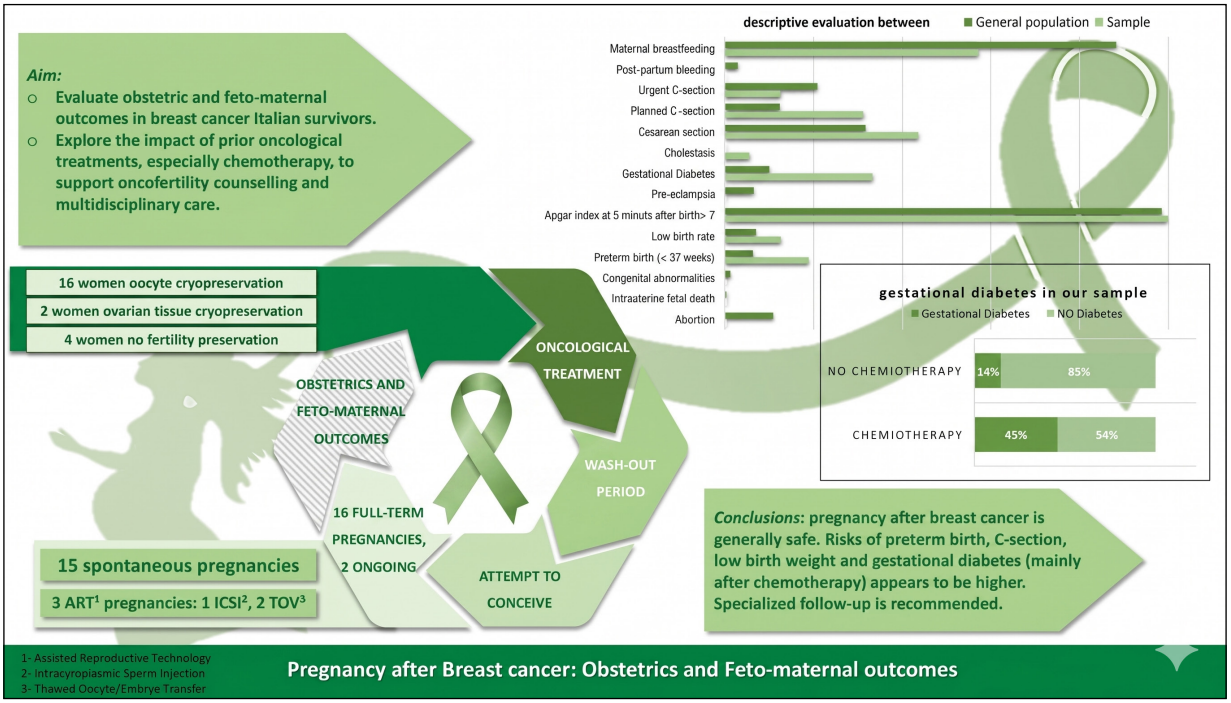

Graphical Abstract. Main findings on pregnancy after breast cancer, highlighting fertility preservation, pregnancy outcomes, and the impact of previous chemotherapy on obstetric and feto-maternal complications.

ed consequences like sexual dysfunction, menopausal symptoms, infertility, and the potential negative impact of family planning. The risk factors for the development of these side effects are age at diagnosis, chemotherapy regimen, and, indirectly, the use of adjuvant endocrine therapy for 5 to 10 years. In the context of increasing maternal age at first pregnancy and the rising incidence of young-onset breast cancer in many countries, a growing number of women are diagnosed with breast cancer before completing their childbearing plans. In recent years, previous scholars[5] have provided important evidence on the safety of conceiving, naturally or after fertility preservation techniques, in young women following anticancer treatment. As widely recommended by international guidelines, a comprehensive and early oncofertility counseling should always be offered[6,7], to acknowledge patients' concerns regarding the desire for motherhood and to improve patient care, thereby avoiding negative outcomes such as nonadherence to adjuvant endocrine therapy and subsequent poorer prognosis[8].

Hartman et al[9] show that pregnancy after BC diagnosis was associated with reduced mortality risk (HR: 0.63; 95% CI 0.51 to 0.79). These data are also confirmed by Moragon et al[10]. Compared to women in the general population, in breast cancer survivors the chances of achieving a pregnancy following treatment are 60% lower. The lack of adequate oncofertility counseling and access to fertility preservation methods can be a possible explanation for these results. Lambertini et al[11], in a recent systematic review and meta-analysis, reported that patients with a post-oncology treatment pregnancy showed both better disease-free survival (DFS) (HR 0.73; 95% CI 0.56-0.94) and overall survival (OS) (HR 0.56; 95% CI 0.46-0.67) compared to women without subsequent pregnancy. This data has been observed regardless of patient characteristics (BRCA mutation status), tumor type (receptor status and lymph node involvement), treatment, and time and outcome of the pregnancy[11].

In patients with hormone receptor-positive breast cancer, the results of the POSITIVE trial provided evidence supporting the safety of temporarily interrupting adjuvant endocrine therapy within the first five years of treatment in women wishing to pursue pregnancy[12]. These results confirmed the safety of temporary interruption of adjuvant endocrine therapy due to pregnancy planning in terms of DFS and OS, highlighting the importance of supporting patients' reproductive choices[12-14].

Limited available evidence suggests that breastfeeding is possible and safe after breast cancer. Azim et al[15] conducted a survey among patients with breast cancer who completed their pregnancy following breast cancer management

to examine their lactation behavior and its effect on breast cancer outcomes. They concluded that breastfeeding did not seem to have any detrimental effect on breast cancer outcomes in survivors who succeeded in completing their pregnancies[15,16]. Furthermore, Sella et al[17] recently published a multicenter prospective cohort study of 94 women interviewed about pregnancy and breastfeeding after breast cancer treatment, concluding that specific research is needed to support breast cancer survivors who wish to breastfeed.

Although the importance of accurate oncofertility counseling in order to preserve fertility prior to breast cancer treatment in women is clear, there is still little data on pregnancy and breastfeeding[18]. For this reason, we investigated maternal and fetal/neonatal outcomes in pregnancies and subsequent breastfeeding among BC patients attending the Physiopathology of Reproduction and Andrology Unit at the Sandro Pertini Hospital in Rome, Italy.

MATERIALS AND METHODS

This is an observational, retro-prospective, longitudinal, single-center study carried out in the Department of Reproductive, Pathophysiology, and Andrology at the Regional Reference Center on Fertility, Oocyte Bank of the Sandro Pertini Hospital, Rome, Italy.

The study was approved by the local Ethical Committee of Lazio 2 (CET Lazio Area 2; IRB protocol number: 0104898/2020, date of approval: 16 June 2020). Informed consent regarding the use of medical information for research purposes was obtained from each participant enrolled in the study, in compliance with local and international legislation (Declaration of Helsinki)[19].

From January 2017 to January 2024, pregnant women with a previous history of breast cancer who had been referred to the Sandro Pertini Hospital were enrolled. None of the 18 patients had comorbidities, with the exception of 1 woman who had an altered glucose metabolism in her past pathological history.

Eleven women underwent chemotherapy treatments: one with Docetaxel + Cyclophosphamide, one with Epirubicin + Paclitaxel, three with Epirubicin + Cyclophosphamide + Paclitaxel, one with Epirubicin + Cyclophosphamide + Docetaxel, two received Epirubicin + Cyclophosphamide + Paclitaxel + Carboplatin, one underwent the protocol with Epirubicin + Cyclophosphamide + Paclitaxel + Carboplatin + Capecitabine, one received Paclitaxel + Trastuzumab, and one received Carboplatin + Paclitaxel. Table I shows the detailed treatment protocols used.

The 18 enrolled women were compared with a control group of healthy women from the general population.

General Italian population data on pregnancies and pregnancy-related complications (including gestation, delivery, fetal diseases, and complications in newborns) were obtained from the Italian National Institute of Statistics (ISTAT)[20] and the Italian Ministry of Health (2019-2022 data)[21]. These data, which collect information on all live births in Italy, cover approximately 1.2-1.3 million births per year. The dataset includes aggregated information on maternal age, parity, type of delivery, and birth outcomes, including birth weight, neonatal complications, perinatal mortality, and cesarean section rates, providing a representative reference population for comparison.

The participants were breast cancer survivors who had completed oncological treatments or had suspended hormone therapy as they tried to conceive. All of them had been referred to

Table I. Pharmacological protocols in the eleven women treated with chemotherapy.

Chemotheraphy (11 pts)	N (%)
Docetaxel + Cyclophosphamide	1 (9.1%)
Epirubucin + Paclitaxel	1 (9.1%)
Epirubucin + Cyclophosphamide + Paclitaxel	3 (27.2%)
Epirubucin + Cyclophosphamide + Docetaxel	1 (9.1%)
Epirubucin + Cyclophosphamide + Paclitaxel + Carboplatin	2 (18.2%)
Epirubucin + Cyclophosphamide + Paclitaxel + Carboplatin + Capecitabine	1 (9.1%)
Paclitaxel + Trastuzumab	1 (9.1%)
Carboplatin + Paclitaxel	1 (9.1%)

our oncofertility center to achieve pregnancy and receive obstetrical follow-up. Prior to the study, all patients received clearance from their treating oncology team to pursue pregnancy. For hormone receptor-positive patients, decisions regarding temporary interruption of endocrine therapy were made according to clinical practice and available evidence supporting pregnancy after breast cancer, including data from the POSITIVE trial[12].

Pregnancies were monitored *via* monthly blood tests and clinical examinations, as well as quarterly ultrasound scans (one ultrasound for pregnancy at 7 to 10 weeks; a second ultrasound to assess fetal morphology at 20 to 22 weeks; a third ultrasound at 30 to 32 weeks to evaluate fetal growth and flowmetry). Every couple received prenatal diagnostic counseling to make an informed decision about whether to undergo non-invasive procedures (Ultrasound screening, Nuchal translucency, NIPT, chorionic villus sampling, and amniocentesis). All patients were advised to undergo a fetal echocardiography at 24 to 28 weeks for early detection of any heart and great vessel defects.

A multidisciplinary team followed patients presenting with pregnancy complications to conduct an obstetric risk assessment and develop a delivery plan. All participants – when possible and in accordance with their wishes – were encouraged to breastfeed. During breastfeeding, they were followed and supported by a team of pediatricians, midwives, and lactation consultants.

Experimental and control groups were compared in terms of pregnancy outcomes, pregnancy complications (for example, gestational diabetes and preeclampsia), delivery outcomes, fetal and neonatal outcomes (such as preterm birth and low birth weight).

Statistical analysis

Using a descriptive method, counts and percentages were reported for categorical variables, and the median and range were reported for continuous variables. Associations between categorical variables were analyzed according to the Pearson Chi-square test or Fisher's exact test, when appropriate. Odds ratios (OR) and their corresponding 95% confidence interval (CI) were derived from the literature to compare/analyze preterm birth, cesarean section, and low birth weight with our study data. The SPSS (version 21.0; IBM Corp., Armonk, NY, USA), a licensed statistical program, and Comprehensive Meta-analysis 3.0 software (CMA; Biostat, Englewood, NJ, USA) were used for all analyses.

RESULTS

Eighteen pregnant women with a previous history of breast cancer were enrolled in the study from January 2017 to January 2024. All patients were evaluated based on their medical history. Median age at diagnosis was 34 years (range 25-42). Median anti-Mullerian hormone levels in our patients before fertility preservation were 2.51 ng/ml (ranging from 0.9 to 5.6 ng/ml). The patients enrolled in the study demonstrated the following oncological features: three (16.7%) with ductal carcinoma *in situ*; fourteen (77.8%) with invasive ductal carcinoma; and one (5.5%) with invasive lobular carcinoma. Four patients (22.2%) tested positive on the sentinel lymph node biopsy. None of the patients presented with distant metastases. For twelve patients (66.7%), the tumor was hormone-receptor positive (HR+) with surface cells showing positive expression of estrogen and progesterone (ER/PR+); eleven patients (61.1%) of malignancies presented with Human Epidermal Growth Factor Receptor 2 (HER2) overexpression; and thirteen women (72.2%) presented tumors with a Ki-67 proliferation index over 15%.

At enrolment, six patients (33.3%) had not been tested for *BRCA1* and *BRCA2* gene mutations; nine (50%) had tested positive for one or both; three (16.7%) had tested negative. Mastectomy had been performed on ten (55.6%) patients (8 patients had a unilateral mastectomy, 2 patients had a bilateral mastectomy), the remaining eight women (44.4%) had undergone a quadrantectomy (or segmental mastectomy). Eleven patients (61.1%) were candidates for neoadjuvant (pre-surgery) or adjuvant (post-surgery) chemotherapy. Seven women (38.9%) had received radiation therapy. Twelve patients (66.7%) had received adjuvant endocrine therapy. Among the 18 patients included in our sample, 14 underwent fertility preservation procedures: 2 (11.1%) underwent ovarian tissue cryopreservation; 12 (66.7%) underwent oocyte cryopreservation, with an average of 8.54 eggs at MII (metaphase-II) preserved in the egg bank at Sandro Pertini Hospital. After oncological treatment, all patients were offered counseling to re-evaluate their ovarian reserve and their pregnancy planning. Seven of the ER/PR+ patients (58.3%) were eligible for suspension of endocrine therapy while attempting to conceive, consistent with criteria outlined in the POSITIVE trial[12]. Indeed, these seven patients discontinued endocrine therapy following clearance from the oncological team. Of these, one was enrolled in the POSITIVE trial.

At the start of their pregnancy journey, the average and median ages among patients were 36.2 and 37 years, respectively (ranging from 29 to 43

years). Average anti-Mullerian hormone values among our patients before the pregnancy journey were 1.13 ng/ml (ranging from 0.0 to 3.56 ng/ml). Twelve patients received adjuvant hormone therapy, with an average of 2.8 years of treatment before suspension for pregnancy research: 9 patients received Tamoxifen therapy, while the other 3 received Letrozole therapy. The average interval between the last oncological treatment and the start of the pregnancy journey was 11.4 months (ranging from 0 to 36 months). The average time to pregnancy was 4.2 months.

Out of 18 pregnancies, 15 (83.3%) occurred spontaneously (assisted *via* follicular monitoring to isolate maximum fertility days and optimize fertilization chances); one was achieved *via* intracytoplasmic sperm injection (ICSI), carried out at the end of the oncological treatment; two were achieved *via in vitro* fertilization (IVF) through the thawing of previously cryopreserved oocytes and subsequent embryo-transfer (ET).

None of the pregnancies resulted in an abortion; two were still ongoing, and the remaining sixteen resulted in the birth of a healthy baby. Although no cases of spontaneous abortion were observed in this small cohort, larger studies are needed to better assess miscarriage risk, given that the estimated rate of spontaneous abortion in the general population is 10.94%. No cases of intrauterine fetal death were observed, compared with an incidence of 0.25% in the general population. Twelve patients (66.7%) experienced a physiological gestation, while six (33.3%) developed a pregnancy complication. Among the six patients with pathological pregnancies, five (27.8%) developed gestational diabetes, and one (5.6%) developed both gestational diabetes and cholestasis. The incidence of gestational diabetes was higher than that reported in the general population (10%), whereas the occurrence of cholestasis was comparable to population data (0.5-2%). No cases of pre-eclampsia or postpartum hemorrhage were observed, compared with reported incidences of 6.5% and 3.0% in the general population, respectively. Thirteen pregnancies (81.2%) resulted in full-term delivery (at 37 weeks or later), while the rate of preterm birth (18.8%) was higher than that reported in the general population (6.3%). Seven patients out of 16 (43.8%) had a cesarean section: five planned, two emergency C-sections, slightly higher than the overall cesarean section rate in the general population (31.8%). Nine patients gave birth vaginally (eight spontaneous deliveries and one Vacuum-assisted delivery). No cases of fetal anomaly nor neonatal pathology were observed, compared with a congenital abnormality rate of 1.1% in the general population. Two infants (12.5%) presented with low birth weight (<2,500 g), a proportion slightly higher than that reported in the general population (7.1%). All newborns achieved Apgar scores >7 (evaluation of the newborn's status at 1 and 5 minutes after birth), consistent with rates reported in the general population (98.5%). Two out of sixteen women giving birth (12.5%) could not breastfeed due to a previous bilateral mastectomy. Eight women (50%) were able to breastfeed unilaterally. Overall, 62.5% of women were able to breastfeed, a significantly lower proportion compared with the general population (88.3%). The median breastfeeding duration was 6 months, ranging between 2 and 22 months.

To identify any possible impact of previous chemotherapy on pregnancy, we compared the incidence of some obstetric and neonatal outcomes in two subgroups of our sample. Our sample was divided into two subgroups: subgroup A included patients who had had adjuvant or neoadjuvant chemotherapy before gestation (n=11 in the group of women who became pregnant, n=10 in the group of women who gave birth); while subgroup B included patients who had not had chemotherapy before gestation (n=7 in the group of women who became pregnant, n=6 in the group of women who gave birth). The data analysis showed a higher incidence of obstetric complications in patients who underwent chemotherapy treatment compared to those who did not. Five patients (50%) and two patients (33%) had a cesarean section, respectively in subgroup A and subgroup B. Preterm birth was experienced by 2 patients (20%) in subgroup A and 1 patient (16.7%) in subgroup B. Low birth weight was observed exclusively in the subgroup A, including 2 patients (20%), while no cases (0%) occurred in the subgroup B. A marked difference was also observed in the prevalence of gestational diabetes mellitus, which was identified in 5 patients (45.5%) and 1 patient (14.3%) in subgroups A and B, respectively.

DISCUSSION

Our results showed that pregnancy after breast cancer does not present an increased risk of miscarriage, intrauterine fetal death, fetal malformations, or postpartum hemorrhage compared to pregnancies of women in the general population.

For comparative purposes, we also evaluated our data alongside those reported by Lambertini et al[11] regarding the incidence of preterm delivery, cesarean section, and low birth weight. Considering pre-term delivery, the OR in our sample was 3.43 (CI 0.98-12.05) *vs.* the OR of the meta-analysis, which was 1.45 (CI 1.11-1.88); for cesarean section, the OR in our data was 2.03 (CI 0.76-5.41),

while in the data of Lambertini et al[11] the OR was 1.14 (CI 1.04-1.25). Finally, for the low-birth-weight infants in our case series, the OR was 1.87 (CI 0.42 -8.22), while Lambertini et al[11] reported an OR of 1.50 (CI 1.31-1.73). Overall, although based on a limited number of cases, our findings appear consistent with the trends described in the meta-analysis (Figure 1).

In our cohort, higher observed rates of preterm delivery and cesarean section were noted compared with those reported in the general population, according to data from ISTAT and the Italian Ministry of Health[20,21].

The analysis of the two subgroups descriptively showed a higher frequency of preterm delivery, cesarean section, and low birth weight infants among women who had received chemotherapy (subgroup A) compared with those who had not (subgroup B). The higher incidence of preterm delivery and low weight at birth was also observed by Anderson et al[22], who reported a higher risk of delivering before the 37th week of pregnancy and of delivering an infant with a birth weight of less than 2,500 g for women with a history of breast cancer who were treated with chemotherapy compared to women in the general population. The study reported a pathophysiological hypothesis based on the potential cardiovascular and pulmonary disorders caused by chemotherapy exposure, which could influence pregnancy outcomes through adverse effects on circulating blood volume regulation. However, the authors also acknowledged that the risk of preterm delivery may be influenced by additional maternal factors, including comorbidities, socio-economic status, and lifestyle habits such as smoking. Regarding pregnancy complications, there is no literature reporting a significant increase in the incidence of pre-eclampsia in the group of women with previous breast cancer compared to the general population. These findings were also confirmed in our sample, with no diagnosis of pre-eclampsia among the women monitored at our center. In the general population, the incidence of this complication amounts to approximatively 6.5%[20,21].

The analysis of our sample showed that patients with a history of cancer had an increased risk of developing gestational diabetes compared to women in the general population. Additional assessment of our sample showed that it was subgroup A, i.e., women who had undergone chemotherapy protocols, who had an increased risk of developing this condition during pregnancy. Evidence in this regard

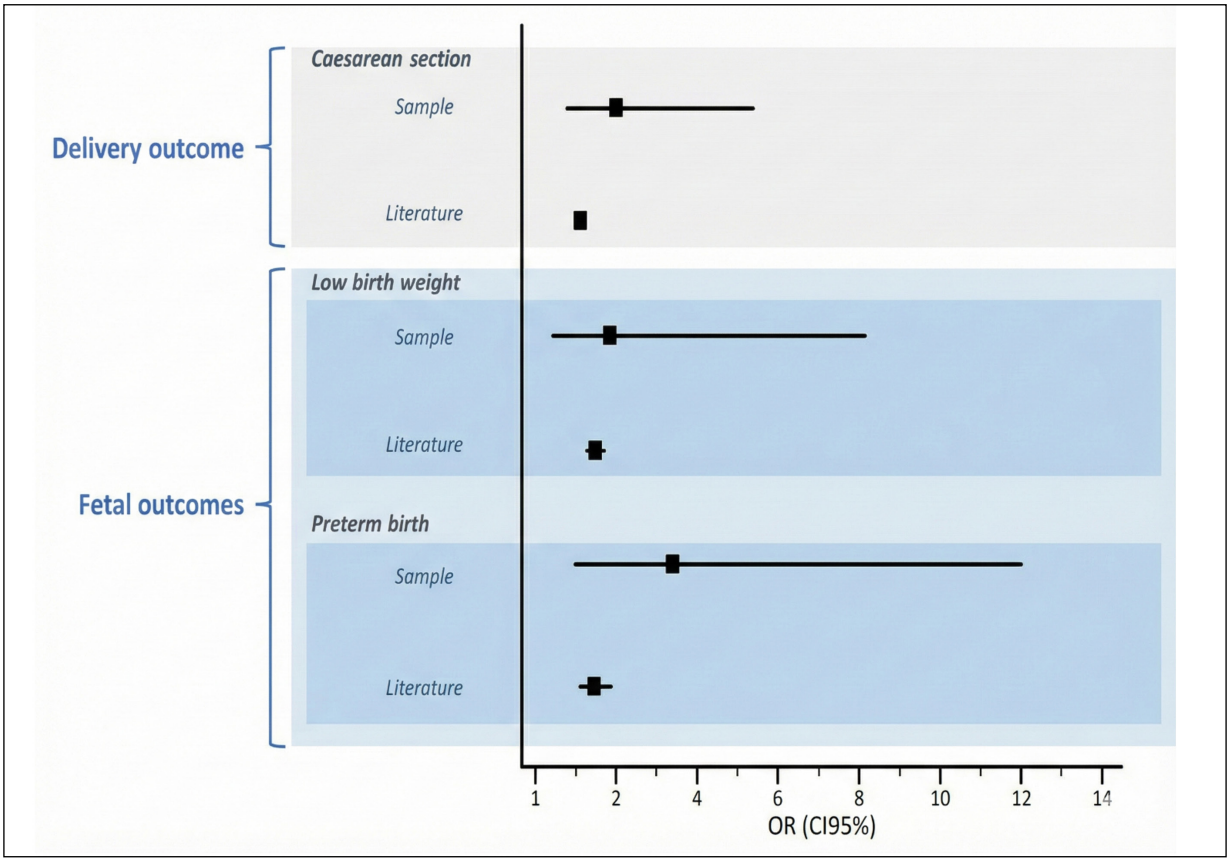

Figure 1. Comparison between the study sample and literature data reported by Lambertini et al[11] on preterm delivery, caesarean section, and low birth weight.

is very limited; therefore, there is no specific reference to the possible correlation between oncological therapies and gestational diabetes, with the only data available focusing on the relationship between cancer treatments and diabetes mellitus. It is known that cancer treatments may worsen glycemic control in patients who are already diabetic or induce transient or permanent hyperglycemia in individuals with normal carbohydrate tolerance prior to cancer diagnosis[23,24]. Both cancer treatments and adjuvant therapies may adversely affect glycemic homeostasis in cancer patients[25,26]. It is now widely acknowledged that chemotherapy agents can affect glucose metabolism by interfering with the synthesis, secretion, and tissue sensitivity to insulin[27,28]. When evaluating the effect of each class of anticancer drugs on glycemic control, a negative impact emerged in patients treated with mTOR inhibitors, cytotoxic antibodies, alkylating agents, anti-microtubules, and antimetabolites. Scholars have attempted to assess the effect of individual chemotherapy drugs on the occurrence of new cases of diabetes[24], although this analysis has proved particularly difficult due to many chemotherapy protocols consisting of a combination of various drug classes, thus complicating the assessment of the impact of single drugs on blood glucose. It is well-known that mTOR inhibitors (such as everolimus, sirolimus, temsirolimus), used in breast cancer, are able to increase insulin resistance and glycemia levels in both diabetic and non-diabetic subjects[29]. There is evidence that immunotherapy drugs, which recently have acquired a relevant role in the treatment of breast cancer, can trigger an immune-mediated response also towards pancreatic β-cells, resulting in destruction of the islets of Langerhans and onset of diabetes in approximately 1% of patients[30,31].

Glucocorticoids, commonly used to reduce the side effects of anticancer therapies or as desensitizers in some cancer protocols, have a well-known adverse effect on glucose homeostasis, leading to increased insulin resistance and hepatic gluconeogenesis, and reduced insulin secretion, thereby increasing circulating serum glucose. Based on these findings, patients who have undergone chemotherapy protocols for breast cancer could be viewed as carriers of 'potential diabetes', defined by Pescetto et al[32] as a condition in which there are definite risk factors for the development of an alteration in glucose metabolism, but not yet clinical manifestations or disturbances such as diagnosed diabetes. Pregnancy as a whole is defined as a 'diabetogenic' condition, as it leads, especially in muscle and adipose tissue, to a progressive reduction in peripheral insulin sensitivity aimed at fetal growth. The higher incidence observed in patients who received chemotherapy, compared with those who did not, may be related to treatment-related effects on glucose homeostasis, including those associated with chemotherapy agents and glucocorticoids used in neoadjuvant and adjuvant settings, although these findings should be interpreted with caution, given the small sample size. It is possible that glucose homeostasis will be restored after the end of therapy, but it may also be possible that women who have received chemotherapy have a lower tolerance to metabolic stress, including pregnancy and the resulting physiological insulin resistance. It is clear that further studies and more data on the impact of chemotherapy on the metabolic homeostasis of these women are needed to confirm this hypothesis, also considering our data showing a higher incidence of obstetric cholestasis in women with a history of breast cancer.

The proportion of women who breastfed in our cohort was lower than that reported in the general population. This is due to the fact that some patients were only able to breastfeed with one breast, following either a unilateral mastectomy or locoregional radiotherapy; also, two patients could not breastfeed at all because they had undergone bilateral mastectomy. Women who interrupted adjuvant endocrine therapy to pursue pregnancy resumed treatment after 24 months to avoid compromising prognosis, resulting in early discontinuation of breastfeeding.

Limitations

Given the small size of our cohort, the comparison with the general population was conducted for exclusively descriptive and exploratory purposes. We acknowledge that differences between the two populations, including operational definitions and underlying clinical characteristics, may introduce bias. For this reason, the comparison was not intended to support inferential conclusions, but rather to provide a contextual frame for our findings in the absence of more suitable control groups.

The data were derived exclusively from a single institution, suggesting that future studies could substantially strengthen the findings by incorporating case histories from multiple centers. Furthermore, the insights gained regarding obstetric pathologies potentially linked to cancer therapies emphasize the critical need for further investigation in the field of oncofertility.

This study provides a basis for further research. Interdisciplinary patient assessment may help clarify the relationship between oncological treatments and reproductive outcomes. Such an expanded research approach will be crucial in addressing the challenges faced by this patient population and shaping clinical practices and guidelines in oncofertility.

CONCLUSIONS

It is important to give breast cancer patients an accurate oncofertility counseling with a multidisciplinary approach that involves not only oncologists and surgeons, but also specialists in reproductive medicine, psychologists, midwives, and pediatricians, to pursue the desire for motherhood, and if their clinical condition permits, to breastfeed their children. Pregnancy in these women does not appear to be associated with an increased risk of miscarriage, fetal intrauterine death, fetal malformations, pre-eclampsia or postpartum hemorrhage, whereas there seems to be an increased risk of cesarean section, preterm delivery, low birth weight, birth of an infant who is small for gestational age, gestational diabetes, especially in those patients who have received chemotherapy. For these reasons, close follow-up in specialized centers is recommended for these pregnancies to improve maternal, fetal, and neonatal outcomes and support breastfeeding. All comparisons presented in this study should be interpreted within a descriptive framework and are intended to generate hypotheses for future, adequately powered studies. Further studies are required to explore the pregnancy outcomes and obstetric complications in breast cancer patients, in order to be able to confirm these preliminary data.

Conflict of Interest
The authors declare no conflicts of interest.

Funding
This research received no external funding.

Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethical Committee of Lazio 2 (CET Lazio Area 2; IRB protocol number: 0104898/2020, date of approval: 16 June 2020).

Informed Consent
Informed consent was obtained from all subjects involved in the study.

Authors' Contributions
All authors contributed substantially to the work reported and have read and agreed to the published version of the manuscript. Cristina Fabiani: conceptualization, project administration, investigation, writing-original draft, supervision. Francesca Sanna: conceptualization, investigation, writing-original draft supervision. Antonella Guarino: conceptualization, project administration, investigation, writing-original draft, supervision. Isabella Sperduti: formal analysis, supervision. Giuliana D'Auria: conceptualization, supervision. Giacomo Corrado: formal analysis, supervision. Teresa Cocchiaro: conceptualization, supervision. Caterina Meneghini: investigation, supervision. Emanuele Licata: formal analysis. Gemma Paciotti: formal analysis. Vincenzo Spina: supervision. Roberta Corno: investigation, supervision. Melania Loggia: investigation, writing-original draft. Cecilia Rucci: investigation, writing-original draft. Andrea Rago: conceptualization, supervision. Rocco Rago: project administration, supervision.

Data Availability
The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

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