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Short inter-pregnancy interval and pregnancy-associated breast cancer

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ABSTRACT

The relationship between pregnancy and breast cancer risk is not fully understood. Most of the literature has described this interaction in terms of the age at first pregnancy and the number of full-term pregnancies. During the prospective accrual of the "Joven & Fuerte: Program for young women with breast cancer in Mexico" cohort, a series of cases with pregnancy-associated breast cancer and a history of a short inter-pregnancy interval was identified. To date, there is a very limited number of descriptions about the interaction between a short inter-pregnancy interval and breast cancer, but none specifically regarding the association of a short inter-pregnancy interval and pregnancy-associated breast cancer. Based on findings from a prospective cohort of young Mexican breast cancer patients, we hypothesize that a short inter-pregnancy interval may increase the incidence of pregnancy-associated breast cancer, possibly by amplifying the effects of the pregnancy-associated factors involved in the development of breast cancer.

Series of cases with pregnancy-associated breast cancer

A total of 552 patients aged ≤40 years with newly diagnosed breast cancer (BC) were accrued in the "Joven & Fuerte: Program for young women with breast cancer in Mexico" cohort between August 2014 and October 2019 at three referral BC centres in Mexico. Forty-three (8%) patients were diagnosed with pregnancy-associated breast cancer (PABC), 19 (44%) during pregnancy and 24 (56%) after pregnancy, with a median age at diagnosis of 34 years (range: 23–40). Seven (16%) patients with PABC had a history of a short inter-pregnancy interval (SIPI), with a median period of 14 months between pregnancies (range: 4–18). Six of them were diagnosed during pregnancy and one after pregnancy, with BC being developed most commonly during or after the third pregnancy (57%). Four of these seven patients were diagnosed at stage I or II and three, at stage III or IV.

The total PABC patients were divided into those with a SIPI and those with no SIPI and a descriptive analysis was performed with the aim of comparing the main clinicopathological features of both groups, which are detailed in the Table 1. Even though the results are merely descriptive given that the number of patients is limited, some relevant findings should be highlighted. All but one of the patients with a SIPI developed BC during pregnancy. In contrast, most patients with no SIPI developed BC after the end of a pregnancy. Age at BC diagnosis was also different between both groups: a median of 31 years was observed among patients with a SIPI, while a median of 35 years was found in those with no SIPI. Likewise, patients' age at first full-term pregnancy also differed, with a median of 27 and 25 years in the SIPI and non-SIPI groups, respectively.

Based on the notable proportion of PABC patients with a SIPI in our cohort, we aim to generate a hypothesis regarding the association of a SIPI with an increased risk of PABC.

Pathophysiology of pregnancy-associated breast cancer

BC is the most common pregnancy-associated malignancy [1,2]; however, the relationship between pregnancy and BC risk is complex and not fully understood. Most of the literature has described this interaction in terms of the age at first full-term pregnancy and the number of full-term pregnancies. Moreover, little is known about the risk factors for PABC, which is defined as BC diagnosed during pregnancy or within

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Table 1
Descriptive comparison between PABC patients with a SIPI and PABC patients with no SIPI.

	Total N = 43 (100%)	SIPI N = 7 (100%)	No SIPI N = 36 (100%)
BC development			
During pregnancy	19 (44)	6 (86)	13 (36)
First trimester	3 (7)	1 (14)	2 (6)
Second trimester	8 (19)	3 (43)	5 (14)
Third trimester	8 (19)	2 (29)	6 (17)
After pregnancy	24 (56)	1 (14)	23 (64)
Pregnancy in which BC developed			
Median (range)	2 (1–6)	3 (2–5)	2 (1–6)
1	9 (21)	0 (0)	9 (25)
2	15 (35)	2 (29)	13 (36)
≥3	19 (44)	5 (71)	14 (39)
IPI (m) N = 34			
Median (range)	48 (4–216)	14 (4–18)	72 (11–216)
Age at BC diagnosis (y)			
Median (range)	34 (23–40)	31 (28–37)	35 (23–40)
Number of children			
Median (range)	2 (0–5)	2 (1–3)	2 (0–5)
Age at first full-term pregnancy (y)			
Median (range)	25 (15–38)	27 (20–34)	25 (15–38)
Clinical stage			
I	2 (5)	1 (14)	2 (6)
II	16 (37)	3 (43)	14 (39)
III	14 (33)	1 (14)	11 (31)
IV	11 (26)	2 (29)	9 (25)
Grade			
1 (3–5)	2 (5)	0 (0)	2 (6)
2 (6–7)	15 (35)	3 (43)	12 (33)
3 (8–9)	24 (56)	4 (57)	20 (56)
Unknown	2 (5)	0 (0)	2 (6)
Subtype			
HR+/HER2-	17 (40)	3 (43)	14 (39)
HR+/HER2+	6 (14)	0 (0)	6 (17)
HR−/HER2+	5 (12)	3 (43)	2 (6)
Triple negative	14 (33)	0 (0)	14 (39)
Unknown	1 (2)	1 (14)	0 (0)
Recurrence			
Yes	7 (16)	0 (0)	7 (19)
No	24 (56)	4 (57)	20 (56)
Not applicable	11 (26)	2 (29)	9 (25)
Lost to follow-up	1 (2)	1 (14)	0 (0)
Vital status			
Alive	33 (77)	6 (86)	27 (75)
Deceased*	7 (16)	0 (0)	7 (19)
Lost to follow-up	3 (7)	1 (14)	2 (6)

SIPI: short interpregnancy interval; BC: breast cancer; IPI: interpregnancy interval; m: months; y: years.
* All deaths were due to BC.

one to two years postpartum [3,4], and which represents a particularly aggressive type of BC [5–7].

It has been reported that BC risk increases transiently for the next 10–15 years after a pregnancy given that it can enhance the expansion of existing clones of malignant breast cells [8]. However, this risk subsequently declines and pregnancy confers a more durable protective effect due to the differentiation of mammary cells induced by full-term pregnancy, which decreases their susceptibility to carcinogenic stimuli [9–13]. Thus, pregnancy has an additional protective effect on BC development by preventing cells from entering early stages of carcinogenesis by reducing the pool of susceptible stem cells.

The reason for the short-term increase in BC risk may be explained by the pregnancy-enhanced proliferation of breast epithelium cells, including those that have undergone the early stages of malignant transformation. This phenomenon precedes and temporarily overcomes the long-term protection conferred by pregnancy through the terminal differentiation of normal mammary stem cells [8,12,14]. Alternatively, the risk might increase secondarily to the effect of high oestrogen levels on pre-existing subclinical cancers [11,12,15]. Although oestriol, the main oestrogen in pregnant women [16], is considered to have a protective effect as opposed to other carcinogenic oestrogens [17], a recent assay on human BC cell lines showed that oestriol triggers a mitogenic effect comparable to that of oestradiol, as well as an upregulation of the expression of oestrogen-responsive genes at culture concentrations similar to those reached by term in maternal serum [18].

Thus, pregnancy may have both, a protective and a deleterious effect on BC development, preventing cells from entering early stages of carcinogenesis by reducing the pool of susceptible stem cells, but also enhancing the development of cancer by expanding existing clones of malignant cells (Fig. 1) [8]. Other gestational hormones may also play an important role in BC development, such as progesterone, which is known to induce the expansion of adult mammary stem cells in mice [19,20]. Likewise, prolactin can promote breast carcinogenesis by enhancing the proliferation and inhibiting the apoptosis of mammary cells, as well as by increasing tissue vascularization [21,22]. In addition, prolactin has been shown to increase oestrogen responsiveness in BC cells [23].

Furthermore, many of the mechanisms that support the normal human pregnancy, including some related to immune tolerance, are also exploited by malignancies to establish a nutrient supply and evade or edit the host immune response. Several immunomodulatory proteins are secreted by trophoblast cells and can be found in maternal peripheral blood. Particularly, the soluble human leukocyte antigen G (HLA-G), expressed on trophoblast and cancer cells, impairs the cross-talk between natural killer and dendritic cells and induces apoptosis of CD8+ cells [24]. In the case of cancer, this effect leads to a down-regulation of anti-tumour immunity and enables tumours' immune escape [24]. Soluble HLA-G has been identified in BC and other solid and haematological malignancies [24]. Additionally, post-lactation mammary involution may also influence T-cell infiltration of the breast microenvironment [25]. Further, high gravidity in mice has been shown to enhance some of the potentially procarcinogenic immunologic effects of pregnancy [26].

Short inter-pregnancy interval and breast cancer

A SIPI is defined as < 18 months between a live birth and the beginning of a following pregnancy [27] and has not been previously correlated with PABC.

It has been reported that women have a transient increase in BC risk after their first pregnancy and a slightly lower increase after their second pregnancy [10]. However, if the period between pregnancies is short, the risk of BC might increase even further, leading to the presentation of cancer during or shortly after the next pregnancy [15]. A previous study reported that young women experienced an increased risk of BC when their first and second births were separated by < 3 years [9]. Another study observed that intervals < 1 year between the first and second, and second and third births were associated with increased risk of BC [15]. Remarkably, for women aged < 50 years, short intervals between the first and second births have been associated with more than a fivefold increase in the risk of developing BC in the following 3 years [28]. This might be explained by a prolongation and an increase of the transient surge in BC risk after the first pregnancy.

Hypothesis

Based on findings from our prospective cohort of young Mexican BC patients, we hypothesize that a SIPI may increase the incidence of PABC, possibly by amplifying the effects of the pregnancy-associated factors involved in the development of BC.

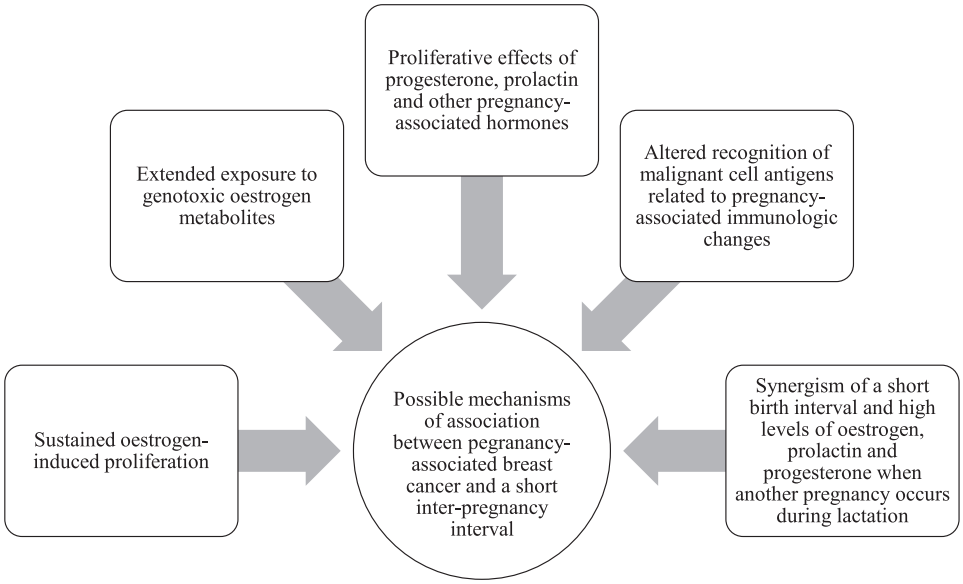

Fig. 1. Factors suspected to intervene in the relationship between a short inter-pregnancy interval and pregnancy-associated breast cancer.

Evaluation of the hypothesis

The evidence from clinical and laboratory data suggest that the mechanisms that could alter the interaction between BC and a SIPI include, but are not limited to, the prolongation of the exposure to high concentrations of oestrogens or their genotoxic metabolites [15,16,29] and the effect of progesterone and other pregnancy-associated hormones on breast tissue [20,30]. Moreover, if a woman becomes pregnant while lactating, the joint presence of high levels of oestrogen, prolactin and progesterone would result in synergic actions after short birth intervals and may facilitate the initiation of breast carcinogenesis [28]. Regarding the immunologic changes that impact on the mammary gland during pregnancy and puerperium, their role linking a SIPI with PABC has not been thoroughly studied yet. The possible mechanisms related to the association between a SIPI and PABC are schematized in the Fig. 1.

Conclusion

According to the phenomena seen in this cohort of young BC patients, we hypothesize that a SIPI may be associated with an increase in the incidence of PABC.

To date and to our knowledge, there is scarce evidence about the effect of a SIPI on PABC, but their association might be especially related to an elevated and prolonged exposure of breast tissue to oestrogen, progesterone, prolactin, and immunologic changes due to two closely consecutive pregnancies. It is worthwhile to further assess the possible relationship between a SIPI and PABC given its implications on the recommendations regarding time frames between pregnancies and the possible benefit of developing training guidelines on thorough breast examinations for obstetricians.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109951.

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