



## Systematic Review

# Phyllodes Tumor of the Breast during Pregnancy and Lactation; A Systematic Review

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## Abstract

**Background:** Phyllodes tumor (PT) is a rare tumor of the breast, which may occur during pregnancy or lactation. Several studies have reviewed and discussed PT occurring in pregnancy, gathering up to 14 patients. We performed a thorough systematic review of the literature in an attempt to find all reported cases, and identify their common characteristics.

**Methods:** We searched Google scholar, PubMed, Ovid Medline, Scopus and ClinicalTrials.gov with several relevant combinations of keywords, looking for texts or abstracts without any date or language limitations, but using only English keywords. The existing literature only consisted of case reports and series; therefore any paper including one or several cases of PT presenting during pregnancy or breastfeeding was recognized as eligible. Articles with vague description of the tumor which made the diagnosis uncertain, and those lacking data about the tumor and management data were excluded. We contacted authors for more details in cases with incomplete information.

**Results:** After excluding those with very deficient data, we included 37 studies, counting 43 cases. The mean age of the patients was 31 years (21-43 years). Some features were different from usual PT: bilaterality (16.2%), large size (14.2 ± 8.6 cm), rapid enlargement (79.5%), and rate of malignancy (60.5%).

**Conclusion:** Our findings show high rates of bilaterality, large size, rapid growth, and malignant pathology in the reported gestational PTs.

**Keywords:** Breast neoplasms, Hormones, Lactation, Phyllodes tumor, Pregnancy

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## Introduction

In 1838, Johannes Muller for the first time described a benign breast mass which had been dormant for a long period and had then enlarged rapidly. He named it Cystosarcoma Phyllodes based on its leaf-like macroscopic appearance, using the Greek word for leaf, *phyllon*. However, various nomenclatures have been used for this entity, including fibrosarcoma, fibromatosum, fibrocystadenoma intracanalicular, giant intracanalicular myxoma of the breast, and many other names.<sup>1,2</sup> Phyllodes tumor (PT) is the term applied by WHO in classification of tumors, and is the most widely accepted designation.<sup>3</sup> The incidence of PT is only 2.1 per million, constituting less than 1% of breast tumors.<sup>4</sup> PT is subdivided into three categories based on microscopic features: benign, borderline and malignant.<sup>5</sup> Clinically, benign PT looks like fibroadenomas,<sup>6</sup> but recurrence after excision of the tumor is much more frequent. Malignant PT, a very uncommon tumor, can be very aggressive with local recurrences and distant metastases.<sup>7</sup>

PT usually presents as a single, rapidly enlarging, firm, mobile, painless mass with circumscribed margins that may grow out of a previously quiescent small mass. The average size of tumors at detection is about 4-5 centimeters,<sup>8</sup> but they can be giant tumors much larger than 10 cm in 20% of cases.<sup>9</sup>

Hormonal changes during gestation affect breasts significantly, bringing about problems in identifying newly formed masses, or affecting the clinical course of existing tumors. Masses may be erroneously recognized as benign changes, and some diagnostic work up may also be postponed in fear of fetal complications, leading to delayed diagnosis and treatment.<sup>10,11</sup> Because of the rarity of this lesion, the influence of pregnancy on the course of PT has not been documented. Also, clinical features, rate of malignancy, treatment and prognosis of the tumor have not been discussed in the literature except for solitary case reports. In order to understand the presentation and course of the disease, we carried out a systematic review to gather all reported cases of PT occurring in pregnancy

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or breastfeeding and find out any specific or common characteristic.

## Materials and Methods

### Inclusion Criteria

Any paper including one or several cases of PT presenting during pregnancy, following labor, or during breastfeeding, written in any language, was included. No date limit was considered.

### Exclusion Criteria

Exclusion criteria consisted of studies where the histology of the tumor was unclear, or the information about tumor characteristics and management of the disease was missing.

### Information Sources

Explored databases and citation indexes consisted of Google Scholar, PubMed, Scopus, Ovid Medline, and ClinicalTrials.gov.

### Search Strategy and Study Selection

We designed a structured protocol (Figure 1) and operated accordingly throughout all steps. A comprehensive search of the literature was accomplished, looking for texts or abstracts without any date restriction or language limitations, but using only English keywords. The combinations we used were: ((breast[Title/Abstract]

AND (phyllodes OR phylloides)) AND pregnan\*[Title/Abstract] in the first round. We repeated the search cycle with other combinations, replacing pregnan\* with gestation\*, lactat\*, and breastfeed\*, and (phyllodes OR phylloides) with cystosarcoma, myxoma, intracanalicular fibrocystadenoma, and fibrosarcoma in separate rounds. Our search in Google Scholar continued until we found irrelevant results in 10 subsequent pages. For other databases including PubMed, Scopus, Ovid Medline, and ClinicalTrials.gov, we explored all the results returned. The non-English, non-French titles were provisionally translated to English using Google translate to assess their relevance.

In the next step, titles and abstracts of all obtained studies were screened, and irrelevant works or duplicates were disqualified. Then, the available English and French fulltexts of potentially relevant articles were reviewed by two authors together, discussing problematic cases; and unquestionable papers were included. Thereafter, the challenging articles were approached. In those which consisted of case series of PTs or of breast lumps diagnosed during pregnancy, and contained a case of PT in pregnancy which had not been fully described, our policy was to contact authors and ask them to provide the required items. Also, in case reports with deficient data, we attempted to get in touch with authors to complete data. In the next stage, we browsed the references of the included papers for

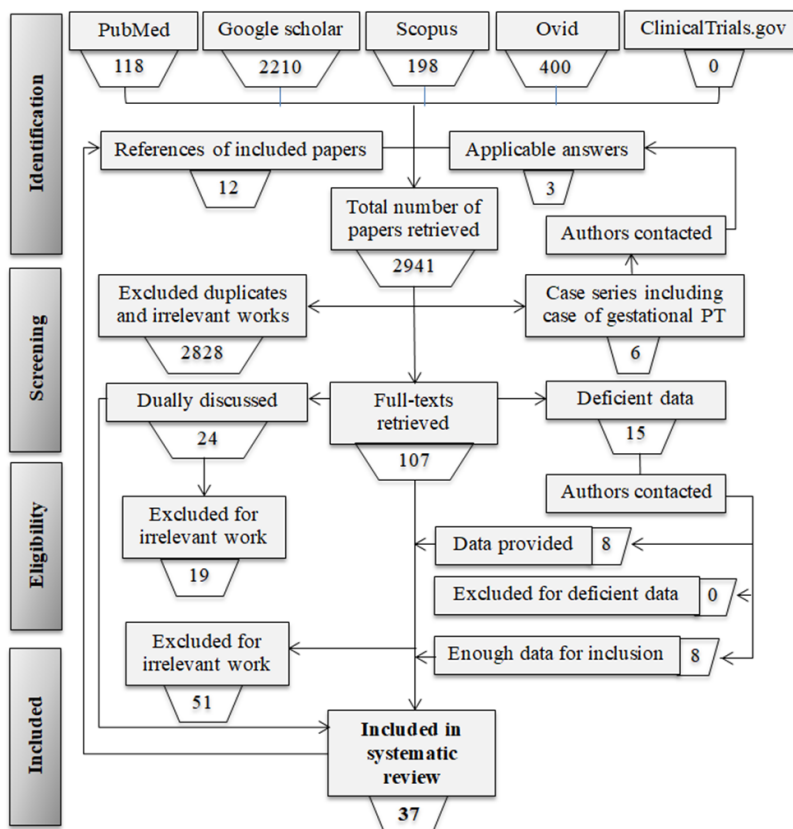


Figure 1. Flowchart of Search Protocol and Study Inclusion.

any study or report not retrieved through our search, and treated the detected literature as above.

### Data Extraction

Data were extracted systematically from eligible papers by two reviewers using a data-extraction form containing all data items (Figure 2). Study features that were recorded in the form comprised first author name, publication year, article title, journal title, and type of study. Data items concerning patients and tumors consisted of age, gestational age/post-partum, lactating status, past breast history, past medical/surgical history, time of onset from first notification, laterality, largest diameter, rapid growth, tenderness, consistency, skin ulcer, skin erythema, axillary lymphadenopathy, other presentation, modes of imaging, ultrasonography findings, mammographic findings, MRI findings, type of breast surgery, type of axillary surgery, chemotherapy, radiotherapy, other treatment, pathology, histology details, follow-up interval from treatment to last visit, patient condition in last visit, and recurrence/metastasis conditions. Definitions of items are shown in Figure 2.

For bilateral cases, two forms were filled out (while omitting study features in the second form). Data were then entered in a Microsoft excel database designed specifically for this study.

## Results

### Search Results

By means of numerous keywords and a sensitive search strategy, we were able to find several case reports, plus reports extracted from the case series. Figure 1 shows the number of articles retrieved in various stages of the search. Date of publication of the earliest and latest relevant articles were 1954<sup>12,13</sup> and 2018,<sup>14,15</sup> respectively. Three articles were in languages other than English and French, consisting of Spanish,<sup>16</sup> Polish,<sup>17</sup> and Portuguese.<sup>18</sup> The

first two<sup>16,17</sup> had English abstracts which were used for data extraction. The other one<sup>18</sup> was translated to English via three online translator software including Google translate (<https://translate.google.com>), Yandex translate (<https://translate.yandex.com/translator>), and SYSTRAN (<http://www.systransoft.com/lp>) in order to obtain a more accurate translation and data.

There were six case series which included one PT in pregnancy each, three of which contained enough data and were included.<sup>12,13,19</sup> The three others contained very limited data about the case.<sup>20-22</sup> We tried to contact the authors in order to obtain more details and succeeded in one case; but they did not have access to data.<sup>20</sup> We could not reach the authors of the other two articles<sup>21,22</sup>; therefore, these three studies were excluded.

### Data Extraction Results

Overall, 37 patients with gestational PT were found in this intensive review of the existing literature. Six of them had bilateral tumors; so, 43 gestational phyllodes are discussed here.

Data were missing in some papers. We made several attempts to contact all corresponding authors and even other authors, except for very old papers, for more details. We were successful in eight cases and completed data correspondingly.

The patients' age and gestational age at time of seeking medical attention, time from onset, past medical histories and family history of cancer, as well as side of tumor and the pathologic type related to malignancy of all included cases are demonstrated in Table 1. All tumors had first presented as a breast lump, except in three patients,<sup>11,18,32</sup> one bilateral and benign,<sup>18</sup> one malignant,<sup>32</sup> and one benign.<sup>11</sup> The first clinical picture in these three was breast enlargement. Table 2 shows clinical characteristics of all benign, borderline and malignant tumors in distinct groups.

Figure 1. Data Extraction Form.

**Table 1.** General Characteristics of All Patients and Tumors

First Author, Year <sup>a</sup>	Age	Gestational Age	Onset <sup>b</sup>	Past Medical History	FH	Side	Type
Andreola 2012 <sup>23</sup>	29	T2	6 m	Osteosarcoma in L jaw 5 y ago	—	L R	Bor Bor
Aranda 2005 <sup>16</sup>	32	T2	1 y	Excision of RB fibroadenoma, 5 and 2 y ago	N	R	Ben
Ariel 1961 <sup>24</sup>	31	PP	—	Excision of RB fibroadenoma, 11 m ago (6 m Gest)	—	R	Mal
Bal 2012 <sup>25</sup>	32	PP	> 1 y	Abortion 1 y ago; excision of Ben PT, same location, 3 y ago	—	L	Mal
Blaker <sup>10</sup> 2010	27	T1	—	Excision of RB fibroadenoma, 7 y ago	—	R	Mal
Cha 2017 <sup>26</sup>	30	PP	—	Vacuum—assisted biopsy of LB fibroadenoma, 5 years ago	—	L	Ben
Chai 2015 <sup>27</sup>	25	T1	2 y	—	—	L	Ben
De Carvalho 1999 <sup>18</sup>	28	T2	4m	—	Y	L R	Ben Ben
Furuya 2012 <sup>28</sup>	32	T2	3 m	—	—	R	Bor
Gentile 2016 <sup>29</sup>	22	T2	8 w	Hemihypertrophy; excision of RB fibroadenoma×2	N	R	Bor
Hernanz 2017 <sup>30</sup>	35	T2	6 m	—	—	L R	Mal Mal
Kallam 2017 <sup>31</sup>	32	T3	8 m	—	N	L	Ben
Kelten 2016 <sup>32</sup>	37	PP	—	—	Y	L	Mal
Lee 2018 <sup>15</sup>	21	—	2 m	Tibial osteosarcoma	—	R	Mal
Lester 1954 <sup>12</sup>	26	T1	1 w	—	—	—	Mal
Li 2008 <sup>33</sup>	27	—	1 y	Excision of RB fibroadenoma×3, from 4 to 2 years ago	—	R	Mal
Likhitmasku 2014 <sup>9</sup>	36	T3	6 m	—	N	L	Ben
Mrad 2000 <sup>34</sup>	32	—	—	—	—	L R	Mal Ben
Murthy 2016 <sup>35</sup>	25	PP	—	—	—	L	Ben
Narla 2018 <sup>14</sup>	28	PP	—	—	—	L	Mal
Nejc 2007 <sup>36</sup>	28	T3	2 m	—	—	L	Mal
Pacchiarotti 2011 <sup>37</sup>	41	T2 <sup>c</sup>	7 m	Infertility	—	—	Mal
Pandit 1985 <sup>38</sup>	32	PP	4 m	—	—	L R	Mal <sup>d</sup> Mal <sup>d</sup>
Pasta 2012 <sup>39</sup>	43	T2 <sup>c</sup>	1 y	Infertility	N	R	Mal
Pytel 2009 <sup>17</sup>	25	T2	2 y	—	—	L	Mal
Ray 2011 <sup>40</sup>	24	T3	9 m	Uterine prolapse; excision of RB unknown mass, 1.5 years ago	—	R	Mal
Reich <sup>e</sup> 1958 <sup>41</sup>	23 <sup>e</sup>	T1	6 y	Excision of RB adenoma, 3 years ago	—	L	Mal
	33 <sup>e</sup>	PP	Recent	—	—	R	Mal
Sharma 2004 <sup>42</sup>	35	T3	3y	—	—	L	Ben
Simpson 2007 <sup>4</sup>	29	T1	7m	Excision of LB fibroadenoma, 3 years ago	N	R	Mal
Testori 2015 <sup>43</sup>	33	4yPP <sup>f</sup>	4y	—	N	R	Mal
Tortoriello 2017 <sup>44</sup>	37	T1	9 m	Abortion at 36 y, under hormone replacement therapy	N	L	Mal
Vergine 2012 <sup>45</sup>	27	PP	a few m	—	—	R	Mal
Vintea 2016 <sup>11</sup>	29	T2	2 m	—	—	L	Ben
Ward 1986 <sup>19</sup>	28	—	A few m	—	—	—	Mal
Way 1998 <sup>46</sup>	35	T3	3 w	—	—	R	Ben
Weledji 2014 <sup>47</sup>	30	PP	11 m	Excision of RB unknown mass, 2 years ago	—	R	Bor
White 1954 <sup>13</sup>	22	T1	—	—	—	—	Mal <sup>g</sup>

Ben, benign; Bor, borderline; FH, family history (of breast cancer); L, left; LB, left breast; Mal, malignant; m, months; N, No; PP, post-partum period; PT, phyllodes tumor; R, right; RB, right breast; T, trimester of pregnancy; T1, 1–12 week; T2, 13–27 weeks; T3, 28–40 weeks; w, weeks; Y, yes; y, years.

<sup>a</sup>year of publication. <sup>b</sup>Onset from first self-detection. <sup>c</sup>Pregnancy after hormonal stimulation due to infertility. <sup>d</sup>PT with osteogenic sarcomatous stroma. <sup>e</sup>Metachronous tumors in 2 breasts. <sup>f</sup>Presented 4 years sooner in pregnancy, but was misdiagnosed as mastitis. <sup>g</sup>adenofibrosarcoma in intracanalicular fibroadenoma as described by Hill & Stout<sup>48</sup>, who had used this term (adenofibrosarcoma) as equivalent cystosarcoma phyllodes.

Ultrasonographic scan was not performed in many cases, namely those related to past times, and thus related features were mentioned in only 23 tumors. Most tumors were circumscribed, and either heteroechoic or hypoechoic, with a predilection for the latter. Of the 15 cases which had described lobulations of the mass on ultrasound, 12 had lobulations, whereas 3 did not; one in each category of benign, borderline, and malignant tumor. Among those explained, margins were irregular in two malignant and

one borderline PT, and regular in 10 others. Vascularity as assessed by Doppler ultrasonographic scan was detected in seven cases, namely in three benign<sup>26,27,31</sup> and four malignant<sup>4,43,45,49</sup> cases.

Management and follow-up of benign, borderline and malignant tumors are shown in Table 3.

The authors of the included papers defined the size of lesions with varying terms. Some reported measured dimensions of tumors, some described largeness of PTs,

**Table 2.** Clinical Presentation of All Tumors

First Author	Clinical Presentation							Tumor Histology		
	Rapid Growth in Pregnancy/Lactation	Largest Diameter (cm) or Mass/Breast Size	Pain or Tenderness	Mass Consistency	Skin Ulcer	Skin Discoloration	Axillary Lymphadenopathy			
Aranda <sup>16</sup>		Y	23, WB	N	Soft	N	Y	N	Benign	
Cha <sup>26</sup>		Y	Huge	N	Hard	N	Y	N		
Chai <sup>27</sup>		Y	20	N	mix <sup>b</sup>	N	N	N		
DeCarvalho <sup>18</sup>	L R	Y	WB	N	-	Y	Y	N		
Kallam <sup>31</sup>		Y	20, WB	N	mix <sup>b</sup>	N	Y	N		
Likhitmasku <sup>9</sup>		Y	20, WB	Y	Firm	Y	Y	N		
Mrad <sup>24</sup>	R	N	10	N	Firm	N	N	N		
Murthy <sup>35</sup>		Y	>Half breast	Y	-	N	N	N		
Sharma <sup>42</sup>		Y	20	-	-	Y	N	N		
Vintea <sup>11</sup>		Y	7.6 <sup>c</sup>	N	Hard	N	Y	N		
Way <sup>46</sup>		Y	5	N	Firm	N	N	N		
Andreola <sup>23</sup>	L R	N	WB -	N	Hard -	N	N	N		Borderline
Furuya <sup>28</sup>		Y	5	N	Soft	N	N	N		
Gentile <sup>29</sup>		Y	19	Y	-	Y	Y	N		
Weledji <sup>47</sup>		Y	10 <sup>e</sup>	N	firm	N	N	N		
Ariel <sup>24</sup>		-	4	Y	firm	N	N	N		
Bal <sup>25</sup>		Y	WB	Y	hard	N	Y	Y		
Blaker <sup>10</sup>		N	-	N	-	N	N	N		
Hernanz <sup>30</sup>	L R	Y	- Half breast	N	-	N	N	N		
Kelten <sup>32</sup>		Y	13 <sup>e</sup>	Y	-	N	Y	N		
Lee <sup>15</sup>		N	-	N	Firm	N	N	N		
Lester <sup>12</sup>		N	4	N	-	N	N	N		
Li <sup>33</sup>		Y	Huge	Y	-	Y	Y	N		
Mrad <sup>24</sup>	L	-	15, WB	N	-	N	N	N	Malignant	
Narla <sup>14</sup>		Y	14 <sup>e</sup>	N	Firm	N	N	N		
Nejc <sup>36</sup>		Y	15	N	Firm	N	N	N		
Pacchiarotti <sup>37</sup>		Y	6 <sup>e</sup>	N	Firm	N	N	N		
Pandit <sup>38</sup>	L R	Y N	6 <sup>i</sup> 2.5 <sup>e</sup>	N N	- -	Y N	Y N	N N		
Pasta <sup>39</sup>		N	1.5	Y	-	N	N	N		
Pytel <sup>17</sup>		Y	-	N	-	N	N	N		
Ray <sup>40</sup>		Y	22	Y	Mix <sup>b</sup>	N	N	N		
Reich <sup>41</sup>	L R	Y	14 27	N N	- -	N N	N N	N N		
Simpson <sup>4</sup>		Y	17 <sup>e</sup>	N	-	N	N	Y		
Testori <sup>43</sup>		Y	40, WB	N	-	N	Y	N		
Tortoriello <sup>44</sup>		Y	24	N	-	N	N	N		
Vergine <sup>45</sup>		Y	10	-	-	N	N	N		
Ward <sup>19</sup>		-	6.5	-	-	-	-	-		
White <sup>13</sup>		-	12	-	-	-	-	-		

L, left; N, No; R, right; UOQ, upper outer quadrant; WB, whole breast; Y, yes.

<sup>a</sup> Multiple masses from 3 to 10 cm. <sup>b</sup> Heterogeneous consistency. <sup>c</sup> Two masses at time of excision, 7 cm and 18 cm. <sup>d</sup> Confluent masses. <sup>e</sup> Size not mentioned in clinic, but in gross histology. <sup>f</sup> multiple nodules form 3–6 cm in left breast in histologic exam.

**Table 3.** Treatment and Follow up of All Tumors

Author	Side	Surgery	Time and Result of Follow up	Histology
Aranda <sup>16</sup>	R	Mastectomy	—	Benign
Cha <sup>26</sup>	L	Lumpectomy	—	
Chai <sup>27</sup>	L	Mastectomy+ reconstruction	10 m, good	
De Carvalho <sup>18</sup>	L R	Bilateral mastectomy	2 m, good	
Kallam <sup>31</sup>	L	Mastectomy	Until now (3 y): good <sup>a</sup>	
Likhitmasku <sup>9</sup>	L	Mastectomy+ axillary dissection+ reconstruction	Until now (6 y): good <sup>a</sup>	
Mrad <sup>34</sup>	R	Wide lumpectomy	17 m: good	
Murthy <sup>35</sup>	L	Wide lumpectomy	3 y: good <sup>a</sup>	
Sharma <sup>42</sup>	L	Mastectomy	—	
Vintea <sup>11</sup>	L	Wide lumpectomy	6 m: good <sup>a</sup>	
Way <sup>46</sup>	R	First: lumpectomy, margin positive; then wide lumpectomy, margin negative	1 y: normal pregnancy 2.5 y: good	
Andreola <sup>23</sup>	L R	L: mastectomy; R: lumpectomy	—	Borderline
Furuya <sup>28</sup>	R	Mastectomy+ axillary sampling <sup>b</sup>	Until now (7 y): good	
Gentile <sup>29</sup>	R	Mastectomy+ reconstruction	—	
Weledji <sup>47</sup>	R	First: wide lumpectomy; then: mastectomy for recurrence	4 m: local recurrence; until now <sup>c</sup> : good	
Ariel <sup>24</sup>	R	Radical mastectomy	6 m: 11 <sup>th</sup> thoracic vertebra metastasis	
Bal <sup>25</sup>	L	Subcutaneous mastectomy+ axillary sampling+ reconstruction	6 m: good	
Blaker <sup>10</sup>	R	First: lumpectomy; margins positive; Then: margin re-excision; margins negative	8 m: good	
Hernanz <sup>20</sup>	R L	RB: subcutaneous mastectomy+ reconstruction; LB: First lumpectomy; then subcutaneous mastectomy for potential residue+ reconstruction	—	
Kelten <sup>32</sup>	L	Mastectomy	—	
Lee <sup>15</sup>	R	Lumpectomy	—	
Lester <sup>12</sup>	—	First: lumpectomy; at 6m: radical mastectomy+ axillary dissection for recurrence	6 m of lumpectomy: Local recurrence; 2 y: widespread metastases, death	
Li <sup>33</sup>	R	First: mastectomy; then: excision and flap for recurrence in chest wall	—	
Mrad <sup>34</sup>	L	Mastectomy	Good	
Narla <sup>14</sup>	L	First: wide lumpectomy; then mastectomy due to residue	—	
Nejc <sup>36</sup>	L	First: lumpectomy; then margin re-excision for mastectomy	20 m: free of disease	
Pacchiarotti <sup>37</sup>	—	First excisional biopsy; then quadrantectomy for Mal	—	
Pandit <sup>38</sup>	L R	LB: mastectomy; RB: lumpectomy	—	
Pasta <sup>39</sup>	R	First: lumpectomy; then: wide lumpectomy for Mal and close margins	1 y: good	
Pytel <sup>17</sup>	L	Mastectomy after 2 y	—	
Ray <sup>40</sup>	R	At 2 m PP: mastectomy	—	
Reich <sup>41</sup>	L R	First: lumpectomy; at recurrence: radical mastectomy Radical mastectomy	14 y of first surgery: death from extensive recurrence <sup>c</sup>	
Simpson <sup>4</sup>	R	First radical mastectomy+ axillary sampling; ChT in early PP+ RT	—	
Testori <sup>43</sup>	R	Radical mastectomy+ axillary dissection	18 m: good	
Tortoriello <sup>44</sup>	L	Lumpectomy with sufficient margin	Until now (2.5 y): good <sup>a</sup>	
Vergine <sup>45</sup>	R	Wide lumpectomy; then mastectomy <sup>d</sup> for histology results+ RT	1 y: good	
Ward <sup>19</sup>	—	First in Py: lumpectomy; after 2 y in breastfeeding: radical mastectomy for recurrence	2 y after lumpectomy: local recurrence; 262 months (22 y): good	
White <sup>13</sup>	—	2 m gestation: lumpectomy; 3 m gestation: mastectomy	3 y: healthy pregnancy and delivery; 8 y: local recurrence; 11 y: good	

ChT, chemotherapy; L, left; LB, left breast; Mal, malignant; m, month; PP, post-partum; R, right; RB, right breast; RT, radiotherapy; w, week; y, year.

<sup>a</sup> Asked and answered by mail, not in article. <sup>b</sup> Surgery postponed because of second Py, then, rapid growth to 15 cm in 3 m, then surgery performed. <sup>c</sup> Extensive locoregional disease in right axilla and right lateral chest wall and widespread metastases in abdominal cavity, spine, and thyroid. <sup>d</sup> defined as compartmental mastectomy in article.

and some others outlined the amount of breast tissue involved by the mass. Clinical size as measured was missing in 13 tumors. The mean size of tumors was  $14.2 \pm 8.6$  cm in the rest. However, we meant to enter most included studies in size scrutiny in order to obtain an estimation of the relation of tumor size to pathologic type. We therefore attempted to combine and unify size definitions, and then classify PTs accordingly. Bearing in mind the range of dimensions and terms used in included studies, the average size of non-gestational PT which is around 4–5 cm,<sup>8</sup> and T staging of breast cancer according to the TNM classification, we defined the following scale: small < 5 cm; 5 cm ≤ medium < 10 cm; 10 cm ≤ large < 15 cm; huge ≥ 15 cm. We could not assign numbers to non-numeric designations; so, we allocated descriptive terms of our self-defined scale to all PTs with any type of size definition. We considered PTs involving half the breast as large and the whole breast as huge. Table 4 illustrates these results as well as main numeric values after excluding missing data, based on pathologic type of tumors.

Skin signs including color changes and ulcerative lesions were mentioned in some case reports, and some studies included images which clearly showed changes in the skin. We considered these characteristics as absent where they were not mentioned or pictured, because clinical findings were defined. All these skin findings are shown in Table 5 in relation to pathologic type of PT.

### Discussion

We performed a systematic review of the literature and collected 43 suitable cases of PT occurring in pregnancy. Previous review articles on this subject consisted of 7 patients (one bilateral: 8 tumors),<sup>10</sup> 9 patients (one bilateral: 10 tumors),<sup>29</sup> and 14 patients (one bilateral: 16 tumors).<sup>35</sup>

The mean age of patients in this study was 31 years (21–43 years), younger than the average of 40–45 years for usual PT<sup>50</sup>; this difference is ordinary because gestational tumors are studied. The youngest patient was 21 and the oldest 43 years old.

The most common presentation of PT is a breast lump, which used to be self-detected previously, and is frequently being detected in imaging recently.<sup>50</sup> This fact also applies to this study, where 90.7% of tumors presented as a mass; and the 9.3% which presented with breast enlargement showed a mass later on.

Due to massive alterations in hormonal milieu such as

the 100-fold and 1000-fold increments in serum estrogen and progesterone, respectively, breasts undergo substantial physiologic changes during pregnancy. Vascular hyperplasia and proliferation of alveoli and lobules cause higher breast volume, weight, firmness, and density; sometimes twice that of the usual breast.<sup>36,51,52</sup> There are two consequences to these: detection of breast lesions becomes difficult both on examination and imaging, and some existing diseases take an altered course, such as hastened enlargement of hormonally responsive lumps.<sup>36</sup> It has generally been said that most gestational breast lumps have indeed occurred before pregnancy but are detected as an expanding or new mass at this time in reaction to hormonal alterations.<sup>52,53</sup> Evidence has not proved that PT is under the influence of steroid hormones, but this theory has been put forward due to reports of rapid enlargement in gravid women.<sup>9,16,36</sup> The reports were not uniform for definition of size of lesions. However, according to our suggested classification (Table 4), most lesions were large or huge. This can be due to the higher probability of large lesions to be detected or reported. Nonetheless, data in Table 4 clarify that size had no relation with pathologic type in these gestational PTs.

In this study, out of 39 tumors which were clinically described, 31 (79.5%) had undergone rapid enlargement during pregnancy or lactation. This represents a high incidence, which highlights the probable dependence of PT on sex hormones. Also, fast growth was seen in 92%, 60%, and 82% of benign, borderline, and malignant tumors, respectively; so, this feature alone might not be much alarming as a signal of malignant behavior during pregnancy or breastfeeding.

No predilection for the right or left breast is expected in PT. Consistently, 20 tumors were in the left and 20 in the right breast in this study; the side of the tumor was not mentioned in three reports. Bilaterality is a rare event in PT, reported in 0.3–3.5% of cases.<sup>3</sup> In our study, 16.2% of patients (6 out of 37) had bilateral disease: five synchronous and one metachronous. This higher

**Table 5.** Breast Skin Changes of All Tumors Based on Pathologic Type

Type (Total)	Skin Ulcer	Skin Discoloration	Skin Changes <sup>a</sup>
Benign (12)	4 (58%)	5 (56%)	7 (58%)
Borderline (5)	1 (14%)	0 (0%)	1 (8%)
Malignant (26)	2 (28%)	4 (44%)	4 (33%)
Total	7 (100%)	9 (100%)	12 (100%)

<sup>a</sup> Skin ulcer and/or discoloration.

**Table 4.** Size of All Phyllodes Tumors According to Pathologic Type

	Mean	Min	Max	Missing	Small (%)	Medium (%)	Large (%)	Huge (%)	Missing
Benign	15.6	5	23	4	0 (0%)	2 (16.5%)	1 (8.5%)	9 (75%)	—
Borderline	9.5	5	19	2	0 (0%)	1 (25%)	1 (25%)	2 (50%)	1
Malignant	13.1	1.5	40	7	4 (18%)	3 (13%)	6(27%)	9 (41%)	4
All	14.2	1.5	40	13	4 (10%)	7 (18%)	9 (23%)	19 (49%)	4

frequency might be incidental, but could also emphasize hormone-responsiveness of PT.

Normally, benign PT is much more frequent than the malignant form.<sup>50,54,55</sup> On the other hand, most breast disorders presenting during pregnancy are benign.<sup>51</sup>

Our study shows a higher frequency for malignant tumors compared to benign ones. Malignant PTs accounted for 26 cases (60.46% of all tumors); among them, three patients had bilateral malignant tumors, while one had a benign PT on one side and a malignant on the other. There were 12 benign tumors (27.90%) including one bilateral, and there were 5 borderline PTs (11.62%), also with one bilateral case. The small number of cases precludes any analysis and conclusion, but this predilection for malignancy cannot be attributed to higher detection rates of malignant disease due to larger size or precipitated growth, because these features were sufficiently frequent in the benign tumors in our study, as well. We hypothesize that female sex hormones might induce malignant transformation in benign PT. Two of the patients affected by malignant PT had become pregnant via hormonal stimulation because of infertility. While this might just be an incidental finding, it may also imply a considerable frequency of high-level hormone exposure, and may be in favor of the above hypothesis.

The onset of disease varied widely among patients in this study, from one week to 6 years, with a mean of 12.8 months. The post-partum period, and then the second trimester of pregnancy were the most common times of presentation. Unexpectedly, onset was shorter for benign tumors, with an average of about 10 months; and longer for malignancies, with an average of around 14 months. We have no explanation for this finding, except that this might imply that malignant cases had long been benign tumors and had undergone malignant transformation through gestational changes, which might be thus in favor of the hypothesis about malignant transformation of benign PT under influence of sex hormones. Here again, the rarity of cases prevents conclusion.

Phyllodes lumps are generally painless.<sup>3</sup> In our study, pain or tenderness was reported in 9 out of 40 PTs; including 2 (17%), 1 (20%) and 6 (26%) benign, borderline and malignant tumors, respectively. This probably illustrates pregnancy-induced mastalgia or associated puerperal mastitis and cannot be determined as a specific feature of gestational PT.

Because of its size and lobulation, PT can lead to stretching and thinning of the overlying skin; ulcers may follow in neglected cases. This can occur in any type of PT regardless of its malignant or benign nature. Skin findings were not more common in malignancy in our study. These appeared in 63%, 20%, and 15% of benign, borderline and malignant cases, respectively. The distribution of skin findings according to type of tumor is shown in Table 5.

Treatment of PT consists of wide local excision of

the tumor to clear margins, without axillary surgery. A margin of 1 cm has been traditionally accepted, and wider resections are recommended for borderline and especially malignant PT. Mastectomy is performed in large tumors, most commonly for borderline and malignant PT, and in recurrent tumors. It is worth noting that newer evidence drives toward thinner margins.<sup>7,54</sup>

In our study, mastectomy was the method of surgery in benign PT for 7 tumors (58.3% of benign tumors), and lumpectomy in 5 (41.7%) of them, including wide margins in 4. We are aware of the follow-up of 6 patients, for an average of 27 months, and a maximum of 6 years. All of them were fine and no recurrence had been detected.

For borderline PT, lumpectomy had been carried out in two and mastectomy in three cases. Recurrence of one of the lumpectomies had been subsequently managed by mastectomy. We also know about the follow-up of that one case, which had no recurrence after more than 5 years.

For malignant PT, 19 mastectomies and 18 lumpectomies had been performed, the latter consisting of quadrantectomy in one and wide excision in two cases. Length of follow-up is known for 13 tumors, and was 65 months on average, with a maximum of 22 years. Local recurrence occurred in three patients at 6 months,<sup>12</sup> 2 years<sup>19</sup> and 3 years<sup>13</sup> after treatment. Distant metastases occurred in three patients at 6 months,<sup>24</sup> 2.5 years (2 years after local recurrence),<sup>12</sup> and 14 years<sup>41</sup> after treatment of the primary tumor. These consisted of solitary bone lesion, widespread metastasis, and both regional and extensive distant metastases, respectively; the latter two resulted in the patient's death. The small number of followed patients and the diversity in extent of tumor and surgery preclude analysis of the association of method of surgery with prognosis. Nevertheless, as would be expected, and supported by these limited data, the course of the disease and prognosis were noticeably worse in malignant cases versus borderline and benign PT.

The effect of systemic endocrine therapy or chemotherapy, as well as radiotherapy, has not been completely defined in the management of PT.<sup>7,9,50</sup> In our study, one patient with malignant PT had undergone both chemotherapy and radiotherapy,<sup>4</sup> and another had received radiation<sup>45</sup> after the operation.

This study had some limitations. We could not contact some authors of published articles which included one case of PT among other cases, and these were excluded. The high rate of malignancy in these gestational PTs could be the result of publication bias, since malignant PT, given their rarity, may be more likely than benign cases to be published as case reports. Furthermore, the sample size precluded formal statistical tests of the hypotheses. We suggest further research on the subject with a large-scale work gathering all PTs reported in the literature, to compare the proportion of malignant PTs in pregnant versus non-pregnant patients.



In conclusion, bilaterality, large size, and rapid growth were more frequent than expected in the reported gestational PTs. However, the size of the tumor and the speed of growth were not associated with higher rates of malignancy in these patients. Because of the high rates of malignancy in gestational PT, and occurrence of two cases of malignant PT following hormonal stimulation for pregnancy in infertile patients, we hypothesize that female sex hormones might induce malignant transformation of benign PT, and propose further research as well as *in vitro* and *in vivo* verification of this idea.

#### Authors' Contribution

SA conceptualized, designed and managed the study; gathered data, wrote the manuscript. AE collaborated in design and data gathering and processing; collaborated in quality control, edited and critically reviewed, and approved the manuscript. FMJ and SF collaborated in collection of data, collaborated in quality control, and approved the manuscript.

#### Conflict of Interest Disclosures

The authors have no conflict of interest.

#### Ethical Statement

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