Desmoid-Type Fibromatosis and Pregnancy

A Multi-institutional Analysis of Recurrence and Obstetric Risk

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Background: Many women who present with desmoid-type fibromatosis (DF) have had a recent pregnancy. Long-term data about disease behavior during and after pregnancy are lacking.

Objective: To investigate the possible relationship between DF and pregnancy.

Patients and Methods: A cohort of women with DF and pregnancy was identified from 4 sarcoma centers. Four groups were identified: diagnosis during pregnancy (A); diagnosis after delivery (B); DF clinically evident during pregnancy (C); and DF resected before pregnancy (D). Progression/regression rates, recurrence rates after resection, and obstetric outcomes were analyzed.

Results: Ninety-two women were included. Forty-four women (48%) had pregnancy-related DF (A + B), whereas 48 (52%) had a history of DF before conception (C + D). Initial treatment was resection in 52%, medical therapy in 4%, and watchful waiting in 43%. Postsurgical relapse rate in A + B was 13%, although progression during watchful waiting was 63%. Relapse/progression in C + D was 42%. After pregnancy, 46% underwent treatment of DF, whereas 54% were managed with watchful waiting. Eventually, only 17% experienced further progression after treatment. Spontaneous regression occurred in 14%. After further pregnancies, only 27% progressed. The only related obstetric event was a cesarean delivery.

Conclusions: Pregnancy-related DF has good outcomes. Progression risk during pregnancy is high, but it can be safely managed. DF does not increase obstetric risk, and it should not be a contraindication to future pregnancy.

Keywords: aggressive fibromatosis, desmoid-type fibromatosis, pregnancy, prognosis, wait and see

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Desmoid-type fibromatosis (DF) is a clonal fibroblastic proliferation marked by infiltrative growth and an inability to metastasize.[1,2] It is a disease that occurs in young adults, such as women of childbearing age, and generally presents an indolent pattern of growth. Historically, management of DF has been surgical resection.[3,4] Nonetheless, surgical approach is often challenging because of the infiltrative nature of the tumor and its location near critical structures. Recently, a more conservative "watchful waiting" approach has been used[5–8] so that DF can be often considered a chronic condition wherein the morbidity of surgery outweighs the risk of disease progression. Although some evidence suggests that DF is modulated by hormonal signaling, the role of specific signaling pathways, such as those mediated by estrogens, is not well understood.[9,10] Indeed, a significant proportion of female patients with a diagnosis of DF have a recent pregnancy history and a new diagnosis of DF has been described during gestation or shortly thereafter. As a consequence, many clinicians evaluating such patients are concerned about potential recurrence or progression during current or subsequent pregnancy and fewer systematic data are available to guide the clinician. The objective of this retrospective study was to analyze the disease-related and obstetric risk associated with DF in a cohort of patients from 4 sarcoma referral centers.

PATIENTS AND METHODS

After approval from our respective institutional review boards, patients were identified from prospective sarcoma databases at 4 referral institutions and medical records were retrospectively reviewed for all female patients evaluated for DF from January 1985 to April 2011. Patients with a recent or subsequent history of pregnancy were included in this analysis. Women with familial adenomatous polyposis (FAP)–related DF and those affected by infantile fibromatosis or palmar/plantar fibromatosis were excluded.

Recent history of pregnancy was defined as a delivery (or abortion) within 6 months before diagnosis of DF or initial diagnosis of primary DF during pregnancy or at the time of delivery. Subsequent history of pregnancy was defined as pregnancy at any time after histological diagnosis of DF, irrespective of the management the patient underwent.

Patients were classified into 4 groups according to the relationship between DF history and pregnancy. Group A: DF diagnosed during pregnancy; group B: DF diagnosed within 6 months after delivery; group C: DF previously diagnosed and still in situ at the time of pregnancy (including previous partial resection); and group D: DF resected before pregnancy without clinical evidence of residual or recurrent disease at the onset of pregnancy. Patients in groups A + B are referred to as women with pregnancy-associated DF, whereas patients in groups C + D are referred to as women with a history of DF.

Histology was confirmed for all patients by an experienced pathologist at each institution, either as part of the initial evaluation of biopsy samples or by reviewing the original slides/blocks. DF was pathologically defined according to World Health Organization criteria as a clonal fibroblastic proliferation developed in soft tissues

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and characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize.[2]

A common data set was established to collect the following elements: age at diagnosis, size of DF at the time of initial presentation (measured as longest diameter), tumor site, initial treatment of DF, date of surgery and margin status (if applicable), recurrence or progression of disease and treatments, date of delivery, type of delivery, and latest follow-up. Recurrence was defined as disease macroscopic relapse 6 months or later after complete resection. Progression, stability, or regression (partial or complete) was defined according to RECIST criteria (version 1.1), whether spontaneous or in the presence of therapy.[11] Tumor site was classified as abdominal wall, extremity (including limb girdle), visceral (including intra-abdominal, pelvic, and mesenteric), or other.

Management of DF included a conservative watchful waiting approach, resection, radiation therapy, isolated limb perfusion (ILP), and systemic treatments. The latter included cytotoxic chemotherapy with any regimen of agents, antiestrogen or LH-RH inhibitors, other hormonal therapy, anti-inflammatory drugs, and targeted biologic therapy. For women with a history of DF, the date and type of first treatment after pregnancy were also recorded, regardless of the initial approach (whether surgical or conservative). All patient care decisions were made at the discretion of each institution's sarcoma service or as part of a clinical trial. Obstetrical complications were also recorded.

RESULTS

Overall, 92 women were identified. Patient and disease characteristics are summarized in Table 1. Median age at the time of DF diagnosis was 31 years (range, 13–40 years), whereas median age at the time of DF-related pregnancy was 32 years (range, 19–45 years). Forty-four women (48%) had pregnancy-related primary DF (groups A and B), whereas 48 women (52%) had a history of DF at the time their pregnancy was confirmed (groups C and D).

The majority of the population had DF tumors associated with their second gestation (n = 54), but DF at the time of first (n = 32) and third gestation (n = 5) was also observed (unknown pregnancy order in 1 woman). Fifteen patients (16%) had at least 1 more gestation after the DF-related pregnancy (1 additional pregnancy in 6 women, and 2 additional pregnancies in 9 women). No patient had more than 3 pregnancies overall.

Anatomic sites of DF were abdominal wall (67%), followed by extremity (17%), viscera (10%), and others (6%). Abdominal wall tumors were noted in 77% of women in groups A and B compared with 58% in groups C and D ($P = 0.0003$), whereas extremity tumors were identified in 7% of women in groups A and B compared with 27% in groups C and D ($P = 0.0003$). In 5 women with abdominal wall DF, the tumors arose within the scar of a previous cesarean delivery. Among the 9 patients with visceral DF, 3 were mesenteric, 4 were intra-abdominal/pelvic, 1 was within the lung, and 1 arose in the vagina. Six patients had multifocal disease. Initial DF treatment was resection in 48 women (52%), systemic medical therapy alone without plan for subsequent resection in 4 (4%), and a conservative watchful waiting approach in 40 (43%).

Disease Outcome

Patient and tumor characteristics and the course of disease over the follow-up period are shown in Table 2, with patients categorized by presentation group. Group A (DF diagnosed during pregnancy) included 24 women, including 5 who received a diagnosis of DF at the time of delivery. Initial treatment was resection in 8 women (2 during pregnancy, 3 soon after delivery, and 3 after neoadjuvant medical therapy), medical therapy in 1 woman, and watchful waiting in 15 women. Twelve of the 15 patients (80%) who underwent watchful waiting experienced disease progression during or after pregnancy; after progression, 4 underwent resection, 4 underwent medical therapy, and 4 remained under watchful waiting. Thus, in summary, after the initial conservative approach (watchful waiting and/or medical therapy), 4 of 16 women required resection. Eventually, 3 of the 24 patients experienced PD after the treatment intended to be definitive (continuous watchful waiting, initial or delayed resection, initial or delayed medical therapy).

Group B (DF diagnosed within 6 months after delivery) included 20 women. Initial DF treatment included resection (n = 7), medical therapy (n = 1), and watchful waiting (n = 12). Five of 13 women (38%) who did not undergo resection experienced progressive disease, all in the watchful waiting cohort; 2 of these underwent resection, 2 received medical therapy, and 1 remained under watchful waiting. Thus, in summary, after the initial conservative approach (watchful waiting and/or medical therapy), 2 of 13 women required resection. Only 1 of the 20 patients experienced PD after the treatment intended to be definitive (continuous watchful waiting, initial or delayed resection, initial or delayed medical therapy).

Group C (DF previously diagnosed and still clinically evident at the time of pregnancy) included 29 women, of whom 10 had recurrent tumors after previous resection. Management of these recurrent tumors was frontline surgery (n = 9) or watchful waiting followed by resection at progression (n = 1). Another 5 women in group C had previously undergone an incomplete intralesional resection and were

TABLE 1. Patients' Characteristic and Initial Treatment According to Referral Institution

	BWH-DFCI	MSH	INT	IGR	Overall Series
No. patients	16	17	24	35	92
Median age at diagnosis (range), yr	31 (22–38)	34 (19–39)	32 (15–40)	33 (13–40)	31
Median age at DF-related pregnancy (range), yr	32 (21–45)	33 (19–39)	35 (26–41)	34 (22–43)	32
Median tumor size at diagnosis (range), cm	7 (3–21)	6 (2–18)	6 (2–35)	4 (1–19)	5
Group A, n	9	7	3	5	24
Group B, n	2	10	4	4	20
Group C, n	0	0	12	17	29
Group D, n	5	0	5	9	19
Frontline surgery, n (%)	12 (75)	1 (6)	7 (29)	24 (69)	44 (48)
Frontline medical therapy, n (%)	3 (19)	1 (6)	2 (8)	2 (6)	8 (9)
Frontline watchful waiting, n (%)	1 (6)	15 (88)	15 (63)	9 (17)	40 (43)

BWH-DFCI indicates Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston, MA; IGR, Institut Gustave Roussy, Villejuif, France; INT, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; MSH, Mount Sinai Hospital and Princess Margaret Hospital, Toronto, Canada.

TABLE 2. Patients' Characteristics, Treatment, and Outcome According to DF-Pregnancy Relationship

	Group A	Group B	Group C	Group D
No. patients	24	20	29	19
Primary site, n (%)				
Abdominal wall	18 (75)	16 (80)	14 (48)	14 (73)
Extremity	1 (4)	2 (10)	11 (38)	2 (11)
Visceral	4 (17)	2 (20)	1 (3)	2 (11)
Other	1 (4)	0	3 (10)	1 (5)
Primary/recurrent, n/n	24/0	20/0	19/10	17/2
Median tumor size at diagnosis (range), cm	7 (2–35)	6 (3–15)	4 (2–25)	5 (1–19)
Progression during or after pregnancy, n (%)	17 (71)	7 (35)	16 (55)	4 (21)
Treatment after progression, n (%)	13 (54)	7 (35)	8 (28)	3 (16)
Surgery	8 (33)	3 (15)	5 (18)	2 (11)
Medical treatment	5 (21)	4 (20)	2 (7)	1 (5)
ILP	—	—	1 (3)	—
DF progression after definitive treatment, n (%)	3 (13)	2 (10)	8 (28)	3 (16)
Spontaneous regression, n (%)	3 (13)	2 (10)	7 (24)	1 (5)
No treatment after initial watchful waiting, n (%)	7 (30)	7 (35)	9 (30)	—

managed with the initial watchful waiting approach. The remaining 14 patients were treated nonoperatively at the time of initial diagnosis (2 by initial medical therapy, 1 by initial watchful waiting followed by medical therapy at progression, and 11 by watchful waiting alone). Sixteen women (55%) experienced progression during (n = 10) or after (n = 3) pregnancy or both (n = 3); 8 of the 16 had active treatment (resection in 5, limb perfusion in 1, and medical therapy in 2), whereas the remainder underwent watchful waiting. Among the 8 managed by active treatment, 2 had further progression requiring either additional surgery (n = 1) or ILP and multiple operations (n = 1); in contrast, none of the 8 managed with watchful waiting needed further therapy.

Group D (DF resected before pregnancy) included 19 patients. Initial treatment before pregnancy was resection in all 19 women (1 patient had neoadjuvant medical therapy). Four patients (21%) experienced local relapse during (n = 3) or after (n = 1) pregnancy, managed by active treatment in 3 women (2 reresection, 1 medical therapy) and watchful waiting in 1. Among the 3 who had active treatment, 1 had further progression requiring additional surgery whereas the 1 woman managed with watchful waiting did not require further therapy.

Taking groups A and B together (ie, pregnancy-associated primary DF), resection was performed in 47% of patients during/after pregnancy. The overall rate of local relapse after initial resection was low at 13% (2/15 patients). In patients with a history of DF (groups C + D), pregnancy was associated with progression/recurrence in 20 cases (42%). For the latter subgroup, resection alone was performed in 7 patients whereas multiple lines of therapy were used in 3 patients.

At a median follow-up of 39 months from pregnancy, 22 women underwent resection after pregnancy (24%), 13 received medical therapy (14%), 6 received medical therapy + resection (7%), 1 was treated by ILP (1%), and 50 were managed with watchful waiting after pregnancy (54%).

Spontaneous regression

In the pregnancy-associated primary DF cohort (groups A + B), 5 women (11%) experienced spontaneous regression (3 partial regression, 2 complete regression). In the cohort of women with a history of DF before pregnancy (groups C + D), 8 women (17%) experienced spontaneous regression after pregnancy (4 partial regression, 4 complete regression). Of note, in 3 women, spontaneous regression occurred after progression during/after pregnancy (7% of the patients who experienced progression associated with pregnancy).

TABLE 3. Obstetric Events

	Group A	Group B	Group C	Group D
No. patients	24	20	29	19
DF-related pregnancy order, n (%)				
First*	4 (17)	7 (35)	15 (52)	6 (32)
Second	19 (79)	13 (65)	12 (41)	10 (53)
Third	1 (4)	—	2 (7)	2 (10)
Type of Delivery, n				
NSVD	11	12	17	10
CS	9	8	2	2
Unknown	3	—	6	6
Abortion, n				
Spontaneous	1	—	2	1
Induced	—	—	2	—
DF-related obstetric events, n				
CS	1	—	—	—
Abortion	—	—	—	—
Subsequent pregnancy				
Yes, n (%)	3 (13)	3 (15)	4 (13)	5 (26)

*One value missing.
CS indicates cesarean delivery; NSVD, natural spontaneous vaginal delivery.

Subsequent Pregnancies

Fifteen women had 1 or more pregnancies after the index DF–associated one (Table 3). After the subsequent pregnancy, only 4 women (27%) needed specific treatment as detailed later.

The first patient had a 17-cm abdominal wall DF diagnosed during her second pregnancy (group A) and was initially managed with watchful waiting. During her next pregnancy, she experienced progression of her existing DF and underwent surgery 36 months after DF diagnosis.

The second patient had a 3-cm abdominal wall DF diagnosed 4 months postpartum after her first pregnancy (group B) and was initially managed with watchful waiting. During her next pregnancy, she experienced progression of her existing DF and underwent surgery postpartum, 13 months after DF diagnosis.

The third patient became pregnant for the second time 4 months after diagnosis of a 3-cm abdominal wall DF initially managed with

watchful waiting (group C). She experienced progression during pregnancy, but not thereafter, and continued watchful waiting. Then, she became pregnant once again and experienced further progression during this third pregnancy. After delivery, she underwent resection at 4 years from DF diagnosis, having experienced progression only during her 2 pregnancies but not otherwise.

The fourth patient had a diagnosis of a 7-cm rectus abdominis DF 6 months after her second delivery (cesarean delivery) and was managed with watchful waiting (group B). Because of progression 9 months after diagnosis, she started hormonal therapy and her tumor growth stabilized.

Obstetric events

DF-associated pregnancy concluded with natural spontaneous vaginal delivery in 40 patients (Table 3). Cesarean delivery was performed in 14 patients but was explicitly because of the presence of DF in only 1 woman.

DF-associated pregnancy ended in abortion in 6 women. Abortion was spontaneous in 4 women and induced in 2 women; in no case was abortion anyway caused by the presence of DF. In 3 women in group D, incisional hernia occurred after delivery in the context of a previous abdominal wall mesh reconstruction; surgical repair was required in 2 cases.

Abdominal wall Desmoid

Overall 62 patients had abdominal wall DF. Among them, 28 (45%) experienced relapse/progression during or after pregnancy; after progression, 22 (35%) were treated with active therapy (14 resection with or without medical therapy; 8 medical therapy alone). Only 3 of all 62 patients with abdominal wall DF (5%) showed progression after the treatment intended to be definitive (continuous watchful waiting, initial or delayed resection, initial or delayed medical therapy).

Special Cases

A 34-year-old woman had a diagnosis of a 7-cm vaginal DF during her second pregnancy. Although her tumor remained stable during pregnancy, she required a cesarean delivery because vaginal delivery was impossible. After delivery, she received hormonal therapy and low-dose chemotherapy and had stable disease 46 months postpartum. She had had no further pregnancies.

A 35-year-old woman had a diagnosis of a 10-cm abdominal wall DF. She underwent medical therapy with antiestrogens. She was lost to follow-up for some months, during which time she became pregnant while on hormone therapy. Without medical guidance, she opted for an elective abortion. She continued to have progressive disease while noncompliant with medical therapy and, ultimately, required resection, without further recurrence.

DISCUSSION

In this international experience, we found that primary DF arising during pregnancy or soon after delivery (groups A and B) is predominantly located in the abdominal wall and generally has an indolent course. In women who have a history of DF when they become pregnant (groups C + D), pregnancy was associated with progression or recurrence in 42%. We have inferred that these 2 categories of DF are best thought of as distinct, and we will discuss them in turn. In fact, we can distinguish between them also in terms of different counseling needed (Table 4).

It remains unclear whether DF progression can be directly attributed to the pregnancy. Of note, within our entire series, no obstetric complications were directly attributable to the diagnosis of DF.

TABLE 4. Available Data for Counseling in Women Affected by Sporadic DF

New diagnosis of DF during or shortly after pregnancy	
Risk of relapse after complete resection	13%
Risk of progression with watchful waiting	63%
Spontaneous regression	11%
Risk of failure after any first active treatment (initial or delayed until the time of progression)	10%
Overall managed without resection	52%
Pregnancy after previous diagnosis of DF	
Risk of DF recurrence/progression	42%
DF recurrence/progression safely managed with either active treatment or watchful waiting	94%
Multiple lines of active treatments needed for progression	6%
Spontaneous regression was described after progression as well	7%
Obstetric risk	
Obstetric complications related to DF in both mother and fetus	0%
Intra-abdominal/pelvic DF should be anyway considered at higher risk (few data available)	
Cesarean delivery to be considered in case of macroscopic DF in particular anatomic sites	
Postpartum incisional hernia after previous abdominal wall full-thickness mesh repair is an issue	

Pregnancy-Associated Primary DF (Groups A and B)

Why pregnancy should influence the development of DF is difficult to establish. Nonetheless, limited evidence suggests a direct association of hormonal status and DF risk: DF incidence is approximately 3-fold higher in women than in men, and among women, it is higher during childbearing years. Furthermore, estrogen, progesterone, and testosterone hormone receptors are expressed in both human and xenograft DF tumor cells,[12–14] and blockade of these receptors appears to result in regression in some models.[15,16] Curiously, in one report of patients affected by FAP, pregnancy had a positive effect on intra-abdominal DF outcome (with lower risk of disease progression in pregnant women).[17]

Indeed, whether pregnancy-associated DF is a distinct entity from sporadic or FAP-associated DF is hard to establish on the basis of its clinical behavior. We found that a substantial proportion of women in our series had DF arising in the abdominal wall (in particular within the rectus abdominis muscle; Table 2), similar to previous observations.[18] However, the presence of DF in the abdominal wall in women of childbearing age during or shortly after pregnancy was not a significant prognostic factor for progression-free survival in a large series of sporadic desmoids as compared with DF at other sites.[7] The high prevalence of abdominal wall tumors in pregnancy-associated DF has also raised speculation about the potential role of trauma from an enlarging uterus on the abdominal wall in the pathogenesis of the disease,[19] although this has not been substantiated in any way. Other observations indicate that DF is promoted by growth factors associated with trauma, and a number of reports describe DF localized to cesarean delivery scars.

Despite any definitive data on the specificity of pregnancy-associated DF, in this subset of patients (groups A + B), we found that outcome is favorable after resection as compared with sporadic DF in general, with a risk of local relapse as low as 13% after initial surgery. In contrast, when a conservative watchful waiting approach was proposed in pregnancy-associated DF, progression was observed in 63% of women whereas spontaneous regression was observed in 11% (in 2 women even despite progression during gestation). The overall rate of spontaneous regression of DF in the entire series of 92 women was higher than expected (14%). Although spontaneous

regression is a well-known phenomenon, it is only reported anecdotally to date.[20–23]

For groups A + B, 52% of patients did not receive resection at any point during their disease course and, instead, could be successfully treated with a conservative approach (watchful waiting and/or medical therapy). In the 2 women who underwent resection during gestation, no significant complication occurred, confirming prior reports.[24] Finally, we found that DF may progress during subsequent pregnancies, but this may be safely managed from both disease and obstetric standpoints. In summary, although pregnancy may influence the development or progression of existing DF, it does not do so in all cases, and even when this occurs, outcomes for the patient and the pregnancy are good.

Women With DF History (Groups C and D)

For the reasons related to hormonal effects as discussed earlier and the potential impact of further pregnancies on pregnancy-associated DF, pregnancy has been often considered a risk factor for recurrence or progression in women with a history of DF.[25] This scenario is investigated in the current series by assessing the women in groups C and D.

DF is often a chronic disease, both because of the significant risk of local recurrence after resection and because of the increasingly frequent application of conservative management.[5,7,8,26] As the watchful waiting approach becomes more common, the risk of DF progression associated with pregnancy is likely to become an emerging issue. In this subgroup, we found progression of DF during/after pregnancy in 42% of cases. Nonetheless, women who experienced progression were successfully treated by resection (35%) or medical therapy, including ILP (20%). The remaining patients opted for watchful waiting even after DF progression; among these, spontaneous regression was ultimately observed in 4 of 9 women.

Therefore, even if the a priori risk of recurrence/progression in the event of pregnancy is significant, it can be safely managed a posteriori in virtually all cases. We were not able to detect any difference among anatomic sites, but more aggressive management may be prudent when DF is located in a challenging or potentially life-threatening site such as mesentery, pelvis, and the head and neck region, although we recognize the challenges inherent to definitive ablation of DF in these anatomic sites. In the subset of women who did not experience DF relapse/progression during pregnancy or thereafter, disease remained under control indefinitely, with a subsequent spontaneous regression occurring in 25% after a median follow-up of 15 months postpartum.

Although we did not observe any obstetric complications in our series, it is nevertheless a potential concern for obvious mechanical reasons in women with an intra-abdominal or pelvic tumor at the time of pregnancy. In addition, our current analysis excludes patients with FAP-related DF and therefore we are not able to comment on pregnancy, as it relates to this population of patients.

One limitation of the present series is that this case mix reflects the policy of 4 major referral centers in Europe and North America over the last 25 years that presents 2 challenges; (1) the initial approach to DF has changed over time, and (2) management differs significantly from one institution to another (Table 1). The main difference was in the policy of initial watchful waiting that became more common in recent years and substantially contributed to the number of patients in group C. Moreover, very few patients with sporadic intra-abdominal DF are present in the series; thus, no conclusions should be drawn from the present study for clinical management of patients with an intra-abdominal/pelvic mass during pregnancy. Nonetheless, this is the first attempt to systematically address the issue of DF and pregnancy, and it sets the landscape for further studies.

CONCLUSIONS

DF progression during or after pregnancy is usually safely managed in experienced centers, sometimes by watchful waiting alone. Therefore, although patients with this condition should be monitored closely, a history of DF should not be an indication for a therapeutic abortion, nor a contraindication to subsequent pregnancy. The relationship between pregnancy and DF is worthy of further analysis to increase counseling expertise at referral centers.

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