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Tenosynovial giant cell tumours

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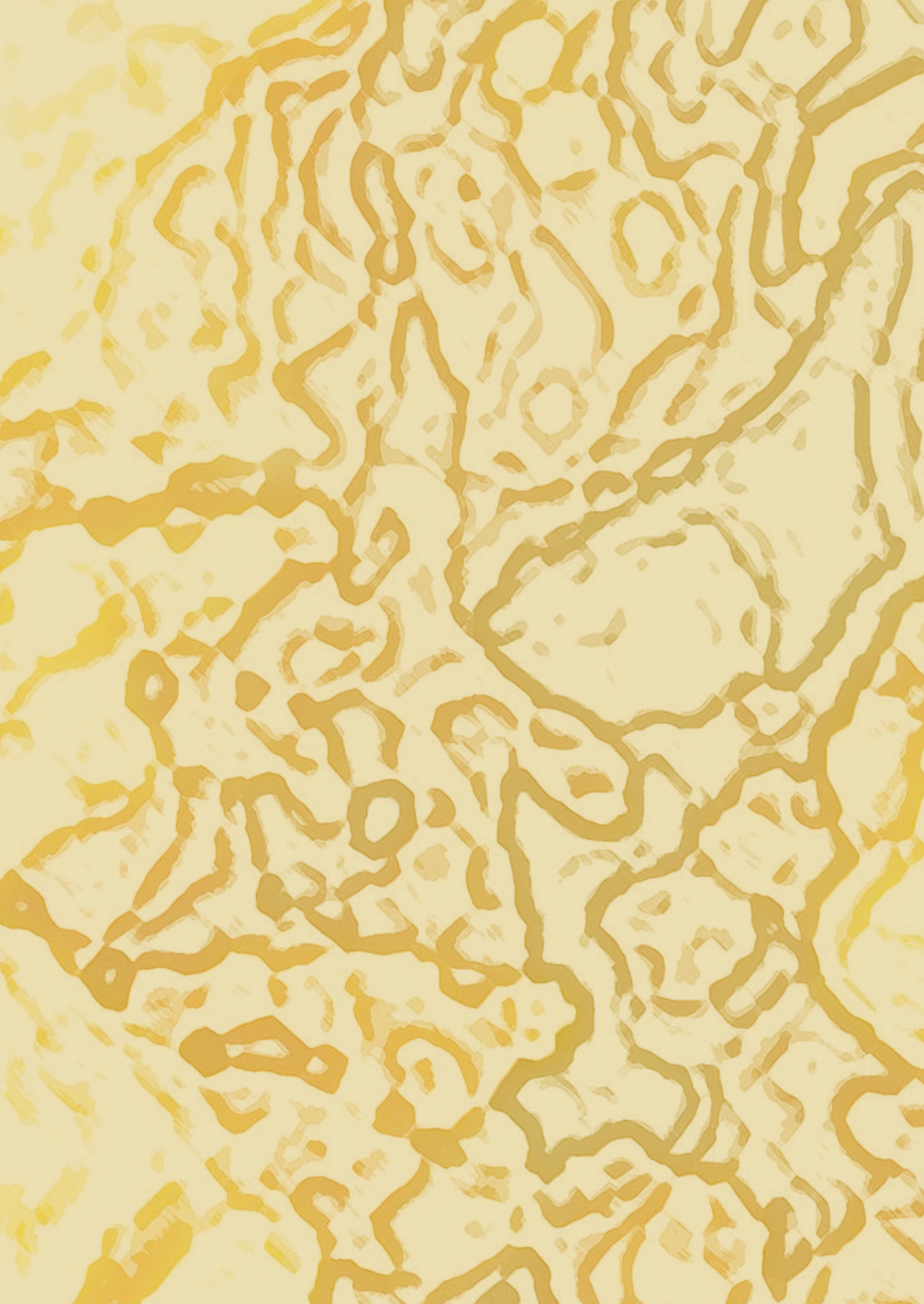


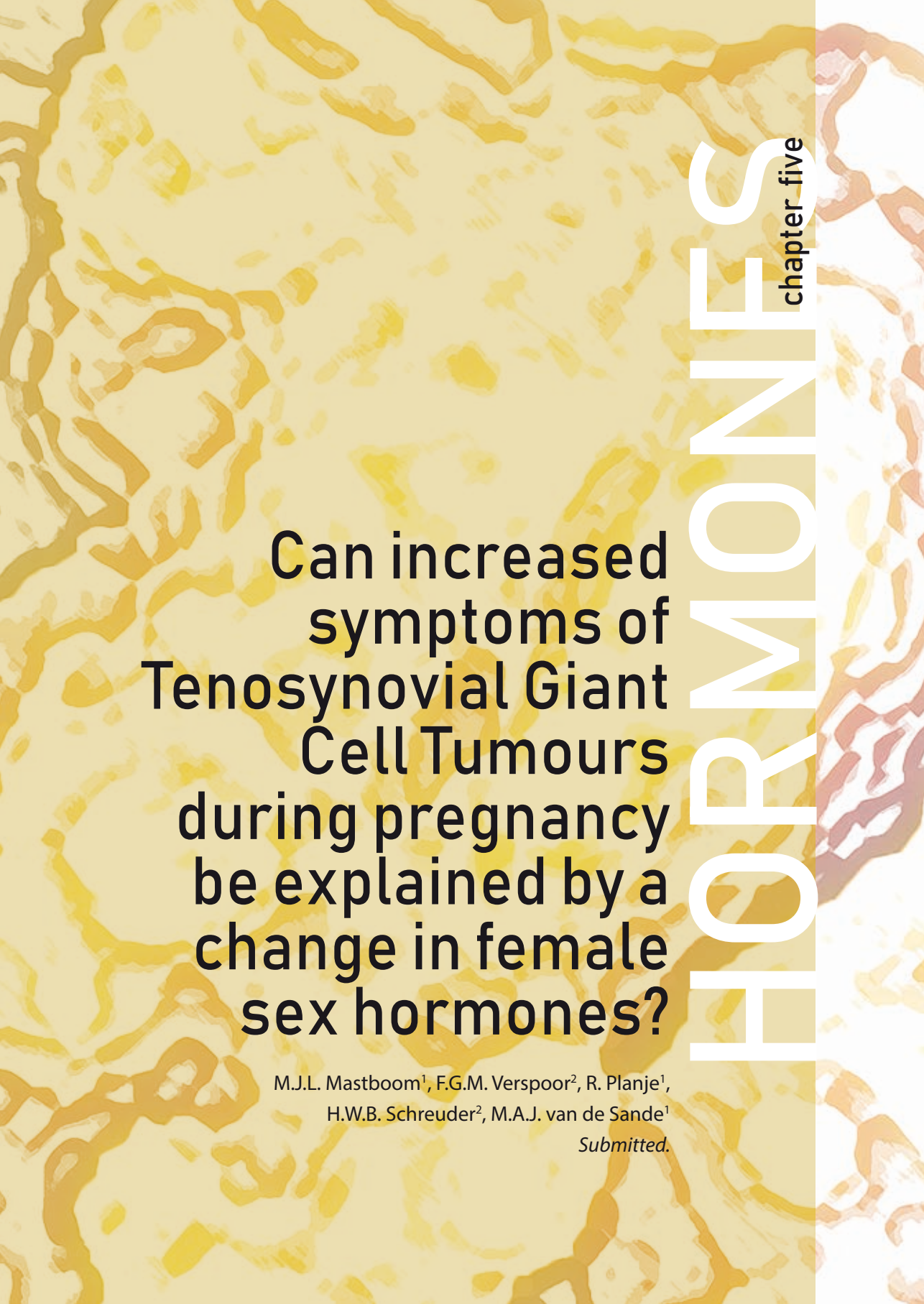
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**Can increased
symptoms of
Tenosynovial Giant
Cell Tumours
during pregnancy
be explained by a
change in female
sex hormones?**

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HORMONES
chapter five

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Abstract

Objective

Tenosynovial Giant Cell Tumours (TGCT), both localized- and diffuse-type, are rare, mono-articular neoplasms, with a slight female predominance. The clinical behaviour between patients differs greatly. This study aims to evaluate the increase in TGCT-related symptoms during pregnancy and the influence of female sex hormones thereon.

Methods

In a prospective-cohort-study, TGCT-related symptoms before and during pregnancy were evaluated in two Dutch centres and by use of the largest online TGCT patient-support group. Second, as a proxy for disease activity the combined TGCT-database of two sarcoma-centres in the Netherlands (N=455) was used to compare recurrence free survival rates between the sexes (during and after fertile-age). Finally, female hormonal receptor status was evaluated with immunohistochemistry on TGCT-specimens from eight women (18-50 years).

Results

Forty percent (8/20) of women with diffuse-TGCT of lower extremity reported an increase in TGCT-related symptoms during pregnancy, predominantly an increase in swelling (62%). Mean VAS-score on symptoms increased between 5.9 (SD 2.1) before pregnancy to 6.6 (SD 1.7) during pregnancy. Similar results were reported in the patient-support group.

No differences were found in recurrence free survival rates, between both sexes, (localized- ($p=0.206 \leq 50$ years, $p=0.935 > 50$ years); diffuse-type ($p=0.664 \leq 50$ years, $p=0.140 > 50$ years)), neither in pre- versus post-menopausal women (localized- ($p=0.106$); diffuse-type($p=0.666$)). In all examined localized- and diffuse-TGCT tissue-samples, oestrogen or progesterone hormone-receptor staining was negative.

Conclusion

An increase in TGCT-related symptoms during pregnancy was reported. This could not directly be linked to female sex hormones as hormone receptors were missing histopathologically. Recurrence free survival rates were comparable, making a relation with female sex hormones improbable.

Background

Tenosynovial Giant Cell Tumour (TGCT), previously known as Pigmented Villonodular Synovitis (PVNS), is a rare, benign neoplasm arising from synovial joints, tendon sheaths and bursae. It affects a relatively young population aged 30-50 years and has a slight female predominance (male:female 1:1.5)¹⁻³. Two subtypes are distinguished. The localized-type is defined as a single nodule, affecting only a distinct area of the synovium with an incidence rate of 10.2 per million person-years (excluding digits). The diffuse-type is known to be more aggressive and involves a larger part or the entire synovial lining. It has an incidence rate of 4.1 per million person-years^{4,5}. TGCT is a mono-articular disease predominantly affecting weight-bearing joints; knee (46% and 64%), hip (1% and 9%), and ankle (5% and 10%) for localized- and diffuse-type, respectively^{3,4}. Pain, swelling, limited range of motion and stiffness of the affected joint are the most common symptoms⁶⁻⁹. Rapid diagnosis is difficult due to these unspecific symptoms and since most physicians are unfamiliar with the disease^{5,10-12}. Arthroscopic or open synovectomy is the standard of care^{1,2,5,8}. After surgical treatment, localized-type in the knee generally follows a favourable course with an average recurrence rate of 4 to 6% after resection (with variable follow-up). In contrast, diffuse-type in the knee presents with multiple recurrences, on average 14% to 40% after surgical treatment⁵.

In TGCT, answers on everyday questions are lacking: e.g. do hormone-based anticonceptiva influence my disease? Does pregnancy influence the clinical behaviour of TGCT? In the outpatient clinic and on online TGCT patient fora, an increase in TGCT-related symptoms during pregnancy is observed. In healthy pregnant women, joint pain in the knee and hip are frequently reported^{13,14}. This pain is not only attributed to the additional weight. Elevated female sex hormones (oestrogen, progesterone and the oestrogen-dependent relaxin) are known to weaken soft tissue structures, resulting in increased joint laxity during pregnancy, joint instability and lower extremity dysfunction^{13,15,16}. To our knowledge, only two case-reports of two pregnant women with both localized-TGCT exist (*supplementary material*). The first case report described a patient diagnosed with TGCT six months after pregnancy completion, as the patient was misdiagnosed with chondromalacia patellae¹⁷. The second patient presented with an acute onset of knee pain during first semester of pregnancy. It was hypothesized that pregnancy-related changes triggered torsion or bleeding of the tumour, leading to this acute presentation¹⁸. Elevated levels of oestrogen

and progesterone receptors have been identified in giant cell tumour of bone, dermatofibroma protuberans and malignancies of breast, endometrium, ovary, prostate, colon. Hormone receptor positive tumours show a better prognosis¹⁹⁻²⁴. The presence of female sex hormone receptors in TGCT is unknown.

This study aims to evaluate patient reported TGCT-related symptoms before and during pregnancy in two different patient populations. Influences of sex specific hormones and female fertile life phase specific hormones are determined by comparing recurrence free survival rates between the sexes and pre- versus post-menopausal women. Finally, presence of female sex hormonal receptor-status in available tumour tissue is assessed.

Methods

Questionnaires in two sarcoma centres and a patient-support group

Patients with diffuse-TGCT were included, since diffuse-TGCT is a more widespread and extensive disease, including more clinical complaints and higher recurrence rates, compared with localized-TGCT.

Two sarcoma centres

One-hundred sixty-two female patients with histopathologically proven diffuse-TGCT were extracted from the combined Dutch TGCT-database (Leiden University Medical Centre (LUMC) N=92 and Radboud University Medical Centre (RUMC) N=70) (*figure 1*)²⁵. Excluded were seventy-four patients <18 years or >50 years, non-weight bearing upper-extremity TGCT (elbow, wrist) or temporomandibular localization. The remaining 88 patients were invited to complete the TGCT-questionnaire. Incomplete questionnaires were unsuitable for analysis (N=26). Finally, sixty-two questionnaires of patients with diffuse-TGCT of lower extremities were included.

The comprehensive TGCT-hormone questionnaire contained questions on patient- and tumour-characteristics, initial TGCT-symptoms (prior to primary treatment), current TGCT-symptoms (symptoms at time of questionnaire completion) and TGCT-symptoms before and during pregnancy. To quantify TGCT-related symptoms, Visual Analogue Scale (VAS) questions were included, ranging from 0 (no symptoms) to 10 (worst symptoms) (*supplementary material*). The pregnancy questions were completed for the first pregnancy (>6 months) after TGCT-diagnosis

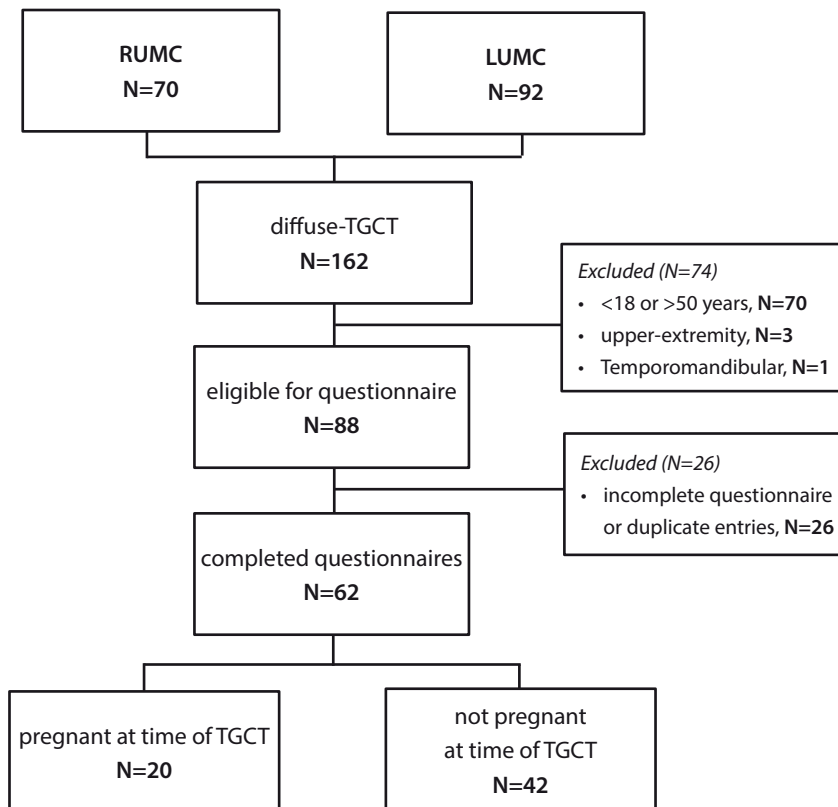


Figure 1 Inclusion flowchart of diffuse-TGCT women, treated in one of two sarcoma centres. RUMC, Radboud University Medical Centre; LUMC, Leiden University Medical Centre.

and questions were answered regarding the TGCT affected joint.

Patient-support group

Previously, an international crowdsourcing study was conducted in 337 patients to evaluate impact of TGCT on daily living²⁶. An e-survey was distributed in the largest, online support group for TGCT-patients: the closed Facebook group 'PVNS is pants!!'. This study contained 129 women with diffuse-TGCT of lower extremity, aged between 18 and 50 years (*figure 2*). Besides patient- and tumour characteristics, the e-survey contained validated questionnaires on physical function and quality of life. Furthermore, questions on TGCT-related symptoms and intensity of symptoms,

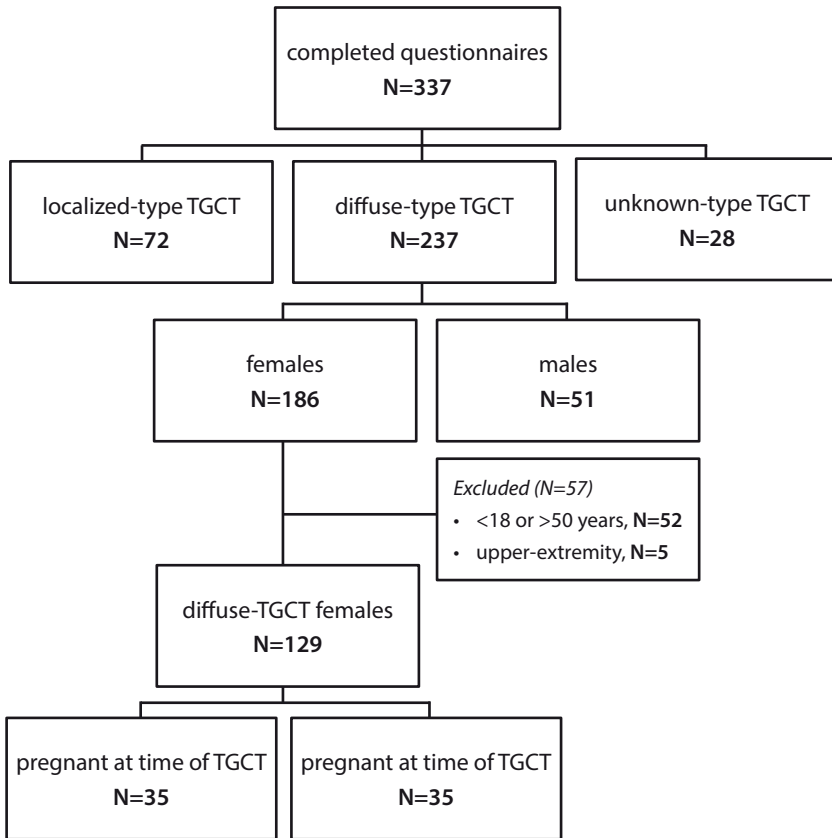


Figure 2 Inclusion flowchart of the patient-support group.

before and during pregnancy were included for women only. These questions were not previously published (*supplementary material*). In more than one pregnancy, questions were answered for the pregnancy that most affected the TGCT-related symptoms.

NetQuestionnaire (NetQ), an online, professional survey software supported by the LUMC, was used to distribute and complete the questionnaires for the two sarcoma centers (eight months available) and the patient-support support group (six months available). Both questionnaires were approved by the institutional review board from the LUMC (comprehensive TGCT-questionnaire study registration number P13.029 and patient support group e-survey study P16.232). NetQ

automatically captured questionnaire-answers into an SPSS 23 file (Statistical Package for Social Sciences statistics (SPSS®) Version 23 (Chicago, IL, USA)), only accessible to TGCT researchers. Unique site visitors were determined by IP addresses. When duplicate entries were detected, the most recent one was included. Statistical analyses were mainly descriptive. To verify that diffuse-type women with increased TGCT-symptoms during pregnancy were comparable with diffuse-type women not pregnant during TGCT in the patient support group, chi-square tests were used for TGCT localization (knee versus hip, ankle and foot), initial surgery (arthroscopy versus open synovectomy), recurrence (yes versus no) and total number of surgeries (1 surgery versus ≥ 2 surgeries). Independent t-tests were used to compare continuous scores of validated questionnaires on physical function and quality of life.

Comparison of recurrence free survival rates

Recurrence was defined as new disease presence after synovectomy or growing residual disease (diagnosed on follow-up MR scan). To determine influences of sex specific hormones and female fertile life phase specific hormones, recurrence free survival rates between the sexes and pre-versus post-menopausal in women were assessed as a proxy. The combined database of two sarcoma centres (LUMC and RUMC) in The Netherlands (N=455, 262 diffuse-TGCT) was used²⁵. This dataset contained all consecutive patients surgically treated for histopathologically proven TGCT between 1990 to 2017. Fertile life phase was defined between 16 and ≤ 50 years at primary diagnosis, since median age at natural menopause ranges between 49 and 52 years²⁷.

Using SPSS®, recurrence free survival rate after index operation was calculated through Kaplan-Meier survival method and log rank test in male and female patients ≤ 50 years and > 50 years for localized- and diffuse-type separately. Similarly, recurrence free survival rates in pre- versus post-menopausal women were compared.

Female hormone-receptors in TGCT

Immunohistochemistry was performed on paraffin-embedded pathological specimens of histopathologically proven TGCT tissue, obtained from eight randomly selected women between 18 and 50 years to determine female hormone receptor status. All samples were of primary resected localized- (N=4) or diffuse-TGCT (N=4), located in the lower extremity (hip, knee, ankle). Monoclonal Rabbit Anti-Human Oestrogen receptor α and monoclonal mouse anti-human

progesterone receptor were used (*supplementary material*). Hormone receptor status was assessed in the LUMC by a dedicated pathologist, specialized in bone and soft tissue tumours. Slides were verified with positive controls of women with oestrogen or progesterone receptor positive breast cancer.

Results

Questionnaires in two sarcoma centres and a patient-support group

Two sarcoma centres

Sixty-two women with diffuse-TGCT of the lower extremities ((knee 50 (81%), hip 6 (9%) and ankle/foot 6 (9%)) with a median age at diagnosis of 30 (IQR 25-38) years completed the comprehensive Dutch questionnaire (*Table 1*). Twenty (32%) patients were pregnant after being diagnosed with TGCT. Eight (40%) of these patients self-reported an increase, two (10%) a decrease of symptoms and 10 (50%) continued at the same level (*Table 2*). TGCT-related symptoms included pain, swelling and limited range of motion of the affected joint, swelling was predominantly increased (62%) (*Table 3*). In patients with increasing symptoms, mostly during second or third trimester (5/8 (63%)) of pregnancy, mean VAS score increased from 5.9 (SD 2.1) before pregnancy to 6.6 (SD 1.7) during pregnancy.

Patient-support group

In 129 women, median age at time of diagnosis was 30 (IQR 24-39) years and TGCT was mostly located in the knee (93 (72%)) (*Table 1*). Thirty-five (27%) women had TGCT during pregnancy. Twenty-three (66%) pregnant women stated an increase, 3/35 (9%) a decrease and 9/35 (26%) did not experience a difference in symptoms during pregnancy. Of all reported symptoms, swelling (57%) of the associated joint increased the most. Additional symptoms included pain, limited range of motion and stiffness (*Table 3*). Self-reported intensity of TGCT-related symptoms after pregnancy was compared with reported intensity of symptoms before pregnancy; in 10/26 (38%) intensity increased, 6/26 (23%) intensity decreased and in 10/26 (38%) intensity continued at a comparable level. No differences were detected in patient- and tumour-characteristics in women with increased TGCT-symptoms during pregnancy compared with women not pregnant during TGCT (*Supplementary material; Table 1*).

Table 1 Tumour- and patient-characteristics of female diffuse-TGCT patients, from two sarcoma centres* and a patient-support group**.

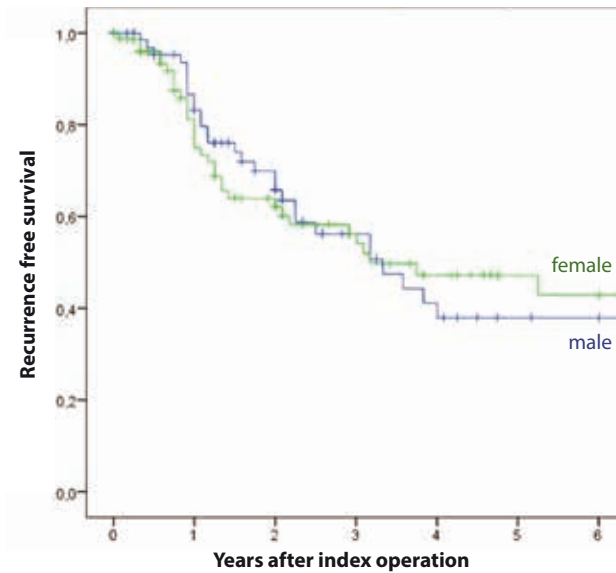
	Sarcoma centres n (%)	Support group n (%)
Total number of women	62 (100)	129 (100)
TGCT-localization		
Knee	50 (81)	93 (72)
Hip	6 (9)	18 (14)
Ankle/Foot	6 (9)	18 (14)
Initial symptoms		
Pain	38 (61)	109 (85)
Swelling	50 (81)	103 (80)
Limited range of motion	32 (52)	83 (64)
Stiffness	22 (36)	74 (57)
Current symptoms		
Pain	36 (58)	98 (76)
Swelling	23 (37)	76 (59)
Limited range of motion	31 (50)	88 (68)
Stiffness	22 (36)	84 (65)
Pregnant >6 months		
Total	20 (32)	35 (27)
Increased symptoms	8/20 (40)	23/35 (66)
Decreased symptoms	2/20 (10)	3/35 (9)
	Median (IQR)	Median (IQR)
Age at time of diagnosis (years)	30 (25-38)	30 (24-39)
Age at time of questionnaire (years)	38 (32-43)	38 (30-45)

Initial symptoms, symptoms of the affected joint prior to primary treatment; Current symptoms, symptoms at time of questionnaire completion. *Leiden University Medical Centre (LUMC) and Radboud University Medical Centre (RUMC). **Largest, online patient support group for TGCT-patients: the closed Facebook group 'PVNS is pants!!'

Table 2 Patient- and tumour characteristics of eight women with increased diffuse-TGCT related symptoms during pregnancy.

Patient	Joint	Age at pregnancy (years)	Time of TGCT diagnosis before pregnancy ⁵ (months)	TGCT treatments prior pregnancy	Most prominent increasing symptom during pregnancy	TGCT treatments after pregnancy	Last follow-up status ⁺⁺
1	Hip	23	84 ⁺	OS + ⁹⁰ Yttrium, OS + cryosurgery	Limited ROM		Residual disease
2	Knee	29	36	2x OS two-staged, OS one-staged + nilotinib + RT 56 Gy	Swelling	EPR	NED
3	Knee	30	24 ⁵⁵	AS	Swelling	AS	NED
4	Knee	31	96		Limited ROM	AS, OS*	NED, osteoarthritis
5	Knee	34	12 ⁵⁵⁵	AS	Swelling	PLX, OS two-staged	Too shortly after OS
6	Knee	34	84	AS	Swelling	2012 OS	Residual disease
7	Ankle	37	2		Pain	OS during pregnancy	Residual disease
8	Knee	38	6		Swelling	OS	NED

TGCT, tenosynovial giant cell tumour; AS, arthroscopic synovectomy; OS, open synovectomy; PLX, PLX3397/pexidartinib; EPR, endoprosthetic reconstruction; Limited ROM, limited range of motion; NED, no evidence of disease. ⁵Pregnancies were uncomplicated, unless otherwise specified. ⁺Pregnancy was prematurely terminated because of major pain complaints of hip. ⁺⁺Last follow-up >2 years since last treatment, unless otherwise specified. ⁵⁵B12 deficiency, right after pregnancy locking of affected knee. ⁵⁵⁵Had to stop TNF- α -inhibitor (indicated for oligoarthritis and Crohn's disease). *Complication: abscess and sepsis.



numbers at risk

male	71	49	32	20	12	8	6
female	84	51	34	25	18	11	9

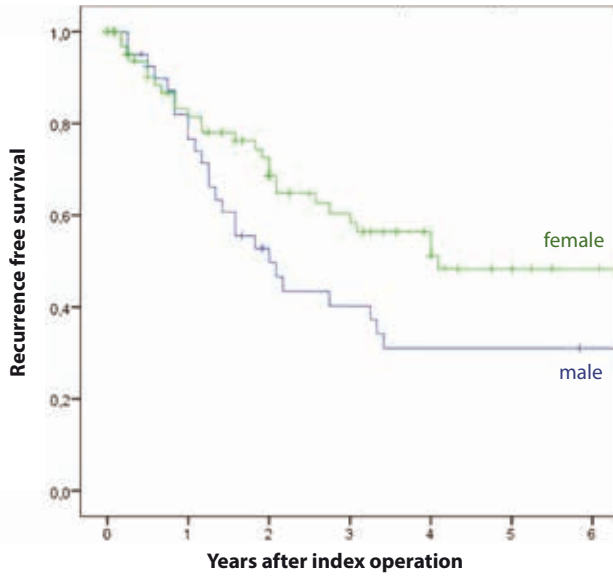
Figure 3 Recurrence free survival curve in 155 diffuse-TGCT patients ≤ 50 years* ($p=0.664$).

*Age at primary diagnosis

Table 3 Most prominent increased TGCT-related symptoms during pregnancy.

	Sarcoma centres n (%)	Support group n (%)
Pain	1 (13)	5 (22)
Swelling	5 (62)	13 (57)
Limited range of motion	2 (25)	3 (13)
Stiffness	0	2 (8)
Total increased symptoms	8 (100)	23 (100)

All patients were requested to indicate which TGCT-symptom increased most during pregnancy. This table presents self-reported increased symptoms in 8/20 (40%) and 23/35 (66%) women with diffuse-TGCT from two Dutch sarcoma centres and the patient-support group, respectively. In both populations swelling was the most prominent symptom.



numbers at risk

male	42	30	17	13	10	10	9
female	65	47	37	28	21	13	11

Figure 3 (continued) Recurrence free survival curve in 107 diffuse-TGCT patients >50 years* ($p=0.140$).

*Age at primary diagnosis



Comparison of recurrence free survival rates

Female recurrence free survival rates were comparable to male rates for localized-type (log rank $p=0.206 \leq 50$ years, $p=0.935 > 50$ years) and diffuse-type (log rank $p=0.664 \leq 50$ years, $p=0.140 > 50$ years) (figure 3). Similarly, in women during and after fertile age, recurrence free survival rates were comparable for localized-type (log rank $p=0.106$) and diffuse-type (log rank $p=0.666$).

Female hormone-receptors in TGCT

All eight localized- and diffuse-TGCT tissue samples were oestrogen or progesterone hormone receptor negative. Further evaluation of additional patient samples was therefore deemed unnecessary.

Discussion

This is the first study to evaluate hormonal influences on the clinical presentation of Tenosynovial Giant Cell Tumour (TGCT). An increase in TGCT-related symptoms during pregnancy was reported, in particular swelling of the affected joint. Recurrence free survival rates were comparable for both sexes as well as for pre- versus postmenopausal women. Oestrogen and progesterone-receptors were not present with immunohistochemistry in TGCT tissue.

In the current study, 56% (31/55) of pregnant patients reported an increase in TGCT-related symptoms and a minority reported a decrease in these symptoms (9%; 5/55). Swelling of the affected joint was self-reported as the most prominent symptom during pregnancy. Since TGCT is a mono-articular disease, this swelling is not comparable with the clinical (bilateral) oedema accompanying a majority of (healthy) pregnancies¹⁴. The increase in symptoms was mainly present during second and third trimester of pregnancy. Similar, healthy pregnancy is associated with an increase in lower extremity symptoms during these trimesters¹⁴. A valid question would be why an increase in mono-articular TGCT swelling during pregnancy would present in these later stages of pregnancy. Since growth hormone is already present five weeks after conception, the question is whether growth hormone influences TGCT-related joint swelling. The experienced increase in disease burden might be caused by progressive disease, but is more likely based on increased effusion. Although pregnancy seems to provoke an increase in TGCT-related symptoms, this might be coincidental according to subjective complaints, recall bias and focus on the affected joint.

In general, a multifactorial aetiology is responsible for lower-extremity symptoms during healthy pregnancy²⁸. First; biomechanical changes, including the anterior shift of the center of gravity¹³, the extra bodyweight²⁹ and a different gait-pattern due to an increased pressure on the lateral side of the foot³⁰, are responsible for lower limb and functional knee pain in pregnant women. As a consequence, a decrease in physical functioning is reported during progression of pregnancy, also in healthy women¹⁵. Second; relaxation of joints is a physiologic process associated with pregnancy. This increased joint-laxity and weakened soft tissue structures is mainly based on the pregnancy initiated elevated levels of the hormone relaxin³¹. Third; discontinuation of medication considered unsafe for the unborn child, for instance non-steroidal anti-inflammatory drugs (NSAID's) or tumour necrosis factor-blockers (TNF- α -inhibitors), might affect the experience of TGCT-symptoms. Additional factors of possible influence on TGCT-related symptoms are nausea/fatigue, stress, emotional/personal problems and anxiousness for additional tasks after pregnancy. The increased TGCT-related symptoms during pregnancy might also be attributed to this multifactorial aetiology for lower extremity symptoms during healthy pregnancy. One (1/8(13%)) patient with increased symptoms interrupted her TNF- α -inhibitor (indicated for oligoarthritis and Crohn's disease) (*Table 2; patient 5*).

To test the hypothesis that female sex hormones influence TGCT, we compared recurrence rates for both sexes. Since oestrogen and progesterone in women decline after fertile age, recurrence free survival rate analyses were performed for both sexes ≤ 50 and > 50 years, without revealing a difference. In accordance with literature no differences in recurrence rates between male and female TGCT-patients were found³². To our knowledge, pre- versus post-menopausal analyses had not been performed before and yielded also no difference.

In all eight primary resected TGCT-tissues, oestrogen or progesterone receptors were completely absent. This is a small sample size, although it is unlikely that positive female sex hormone status will be detected by evaluating additional specimens. Hormone-based anticonceptiva or female hormone based treatments do not seem to influence the clinical behaviour of TGCT. Future research is recommended to find the cause of increased symptoms in TGCT during pregnancy and to contribute to possible new treatment modalities, e.g. growth-factor, ED-A fibronectin (expressed during embryogenesis) or changes in the auto-immune system.

Evaluation of hormonal influences in TGCT is challenging because of the rarity of the tumour and the heterogeneous patient population. Main limitation in our two questionnaire studies was participant recall bias. Information provided on a recall basis diminishes the accuracy of results. Preferably, an observational study would be performed, including a control group and radiographic evaluation of tumour severity before and after pregnancy. Furthermore, answers from the e-survey in the patient support group could be influenced by multicultural differences. Finally, while previous surgeries provoke deteriorated clinical outcome, treatments before pregnancy and treatment phase during pregnancy were not taken into consideration.

Conclusion

In conclusion, an increase in TGCT-related symptoms during pregnancy was reported in two different patient cohorts. This could not directly be linked to female sex hormones as hormone receptors were missing histopathologically. Recurrence free survival rates between both sexes and between pre- versus post-menopausal women were also comparable, making a causal relation with female sex hormones even more unlikely.

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