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Management of musculoskeletal tumors during pregnancy: a retrospective study

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Abstract

Background: In recent years, scientific research has increasingly focused on malignancies during pregnancy. However, the development of musculoskeletal tumors during pregnancy has only been the subject of a few studies so far. The primary aim of this study was to identify the incidence of sarcomas during pregnancy at our musculoskeletal tumor center (MSTC). Secondarily we intended to analyze these cases and discuss possible recommendations regarding diagnostic work-up as well as therapy on the basis of the literature.

Methods: All female patients who had been treated for soft tissue or bone sarcoma at our academic MSTC in the period between the years 2002 and 2010 were screened retrospectively for anamnestic annotations of pregnancy or records of pregnancy in the obstetrical database of our university hospital. The patients who met the criteria for inclusion (diagnosed sarcoma and pregnancy) were enrolled. For every pregnant patient two age-matched female control patients that suffered from tumors with the same histologic type were included.

Results: In the period between 2002 and 2010, 240 female patients between the age of 16 and 45 were treated for sarcoma. In eight out of the 240 cases the tumor disease developed or progressed during pregnancy. The delay in diagnosis was approximately eight months and turned out to be significantly higher for pregnant patients compared to non- pregnant controls. Each woman's tumor was misdiagnosed at least once.

Conclusions: Diagnostic follow-up of pregnant women presenting with a growing or painful mass, which is suspected to be a musculoskeletal tumor, should be performed at a specialized tumor center. We recommend a multidisciplinary approach and discussing all possible consequences for mother and child intensively in accordance with the available literature.

Keywords: Pregnancy, Sarcoma, Musculoskeletal tumor, Lower extremity, Recommendations

Background

In recent years, scientific research has increasingly focused on malignancies during pregnancy. Although several publications provide initial evidence that pregnancy most likely affects the growth and/or development of a tumor, reports are scarce and further research is necessary [1–3]. Cancer is reported to occur in approximately 1 per 1000 pregnant women [4–6]. As women tend to delay pregnancy to older ages, the incidence of cancer during pregnancy will likely increase [7]. While breast cancer is the most common malignancy in pregnancy [5], the incidence of musculoskeletal tumors during pregnancy is comparably low. These tumors have only been the subject of a few studies so far. While Maxwell et al. [8] focused on the outcome, an Israeli group [9, 10] reported on its experience in treatment of musculoskeletal tumors twice. Guidelines regarding the clinical diagnostics and acceptable as well as justifiable treatment of musculoskeletal tumors during pregnancy still do not exist. Due to the rareness of tumors during pregnancy, guidelines could not be issued so far, but it is important to discuss these cases and to contribute data to the literature.

Therefore, the primary aim of this study was to identify the incidence of sarcomas during pregnancy at our musculoskeletal tumor center (MSTC). Secondarily we

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intended to analyze these cases and discuss possible recommendations regarding diagnostic work-up as well as therapy on the basis of the literature.

Methods

All female patients who had been treated for soft tissue or bone sarcoma at our academic MSTC between 2002 and 2010 were screened retrospectively for anamnestic annotations of pregnancy or records of pregnancy in the obstetrical database of our university hospital.

The patients who met the criteria for inclusion (diagnosed sarcoma and pregnancy) were enrolled according to the guidelines of Good Clinical Practice (GCP). For every pregnant patient two age-matched female control patients that suffered from tumors with the same histologic type were included. Therefore this retrospective case–control study was designed to have a 2:1 matching. The study was approved by the Medical Board of Ethics of the Technische Universitaet Muenchen (reference no. 4092/11). From each patient written informed consent was obtained to publish their data and information. The patient records were anonymized prior to analysis. The previously treating institutions or private practices were contacted to obtain the prenatal records of the patients. Furthermore, our own database and documentations on each patient for detailed information about the patient and the patient's diseases was reviewed.

The tumor staging was based on the 6th and 7th edition of the UICC TNM staging system (Union internationale contre le cancer) and the grading of the soft tissue sarcomas was based on the FNCLCC (Fédération Nationale des Centers de Lutte Contre le Cancer) grading system [11]. We performed statistical and mathematical calculations and analyses (such as the arithmetic mean or percentages) with the SigmaStat software (SigmaStat 4.0, Systat Software Inc., Chicago, Illinois, USA). For the comparison of continuous quantitative data the Welch's *t*-test (two-sample unpooled *t*-test for unequal variances) was performed with the QuickCalcs software (GraphPad Software, Inc. La Jolla, California, USA) after ensuring normal distribution of data with the Kolmogorov-Smirnov test using SigmaStat software (SigmaStat 4.0, Systat Software Inc., Chicago, Illinois, USA). For the comparison of categorical data the Fisher's test was performed with the QuickCalcs software (GraphPad Software, Inc. La Jolla, California, USA).

Results

Patients

In the period between 2002 and 2010 240 female patients between 16 and 45 years of age were treated at our MSTC for sarcoma. Anamnestic annotation of pregnancy was found in eight of these cases (3.3 %). The patients' age at the time of diagnosis ranged between 26 and 40 years, with a mean age of 30 ± 4 years. The patients gave birth to three male and four female babies. The sex of the 8th fetus remains unknown due to a spontaneous abortion in the first trimester.

Sixteen control patients with the same histologic tumor types were included. Their age ranged between 25 and 41 years with a mean age of 29 ± 4 years.

Diagnosis

Four of the eight patients noted the first symptoms or signs of a tumor at a menstrual age of 34.5 ± 3 weeks according to prenatal records. In four cases a precise date for the onset of symptoms could not be determined according to medical records, but three patients could report a time period (menstrual age of 32 to 35 weeks, 14 to 18 weeks and 27 to 32 weeks). In the remaining case the onset of symptoms could not be investigated. In all cases pain, a growing mass or a limitation of motion was the clinical presentation of the sarcoma. The patients consulted an average of 4.5 ± 2.7 different doctors until the diagnosis of sarcoma was made at our musculoskeletal tumor center. From the first consultation to the correct diagnosis it took a mean of 8.0 ± 2.3 months. Six of our eight patients stated that there was a hesitancy to perform imaging during pregnancy. In five of these cases imaging was performed within one week postpartum. In the remaining case imaging was delayed until six weeks postpartum. In only one case a magnetic resonance imaging (MRI) exam was performed before referral to our MSTC, while a biopsy was performed in three cases. Three patients had undergone a biopsy before referral to our tumor center. All of them led to a wrong diagnosis (benign tumors) – most likely due to non-representative tissue sampling. After performing further biopsies in our tumor center we diagnosed the sarcomas. Unfortunately, the disease was already advanced in two cases and we had to perform a rotationplasty in the first and amputation above the knee joint in the second case. Due to her concerns about the fetus, one patient refused to have any diagnostic procedure done during pregnancy (imaging, biopsy). After delivery, a hemipelvectomy was necessary.

Each woman's tumor was misdiagnosed at least once (for diagnosis details see Table 1).

In all cases the sarcoma had developed at the lower extremity. Three synovial sarcomas, one Ewing's sarcoma, one clear cell sarcoma (soft tissue), one chondroblastic osteosarcoma, one liposarcoma and one fibrosarcoma were diagnosed at our MSTC. In all cases the tumor size was considerably large with a mean maximum dimension of 11.1 ± 4.6 cm and a mean tumor volume of ~620 cm^3.

The UICC staging results and the FNCLCC grading results show that the malignancies were mainly resected in a comparatively late stage (for detailed tumor information see Table 2). The control patients consulted an average of

Table 1 Diagnosis details

	First symptom	Pregnancy number	Site and size	Histology	Grading and staging	Progression in pregnancy	Pregnancy Outcome: delivery; birth weight; gestational age; sex of fetus; APGAR Score	Treatment	Treatment timing
I	Pain noticed in the period between the25th to the 30th week of pregnancy[a], later tumescence	4th in 2009	Knee joint (right); 16,5x9x12	Synovial sarcoma	G3; pT2b, pNX, pMX Δ	Increasing pain and tumescence in the last few weeks of pregnancy, afterwards stable symptoms	Cesarean (due to the patients wish); 2750 g; 36th week; male; 9	Marginal tumor resection	8 months postpartum
II	Pain which occurred in the 37th week of pregnancy	2nd in 2009	Fibula dist. (left); maximum of 9 cm	Ewing's sarcoma	G3; ypT2 ◊	Walking problems which occurred in the 39th week	Vaginal delivery; 3140 g; 40th week; male; 10	En-bloc resection	11 months postpartum
III	Painful swelling noticed in the 31th week of pregnancy	2nd in 2010	Knee joint (left); 13x10x5,5	Clear cell sarcoma, soft tissue	[b]; pT2b, pN1(2,6), pM1 (OSS) ◊	Increasing pain until treatment	Cesarean (due to the patients wish); 3320 g; 40th week; female; 10	Rotation-plasty	6 months postpartum
IV	Pain which appeared in the period between the 30th to the 33th week of pregnancy[a]	1st in 2004	Upper ankle joint (left); 3x2,7,x1,5	Synovial sarcoma	G2; pT1b ◊	-	Vaginal delivery; 3070 g; 38th week; female; 10	En-bloc resection	4,5 months postpartum
V	Pain noticed 32th week of pregnancy	2nd in 2002	Femoral head (left); 16x9x8 after neoadjuvant chemotherapy	Osteosarcoma chondrobl.	G3; pT2, pNX, pM1 (Oss)	Increasing pain until treatment	Vaginal delivery; 3450 g; 41th week; female; 9	Hemi-pelvectomy	4 months postpartum
VI	Pain which occurred between the 12th-16th week of pregnancy[a]	4th in 2007 [spontaneous abortion]	Thigh med. compart. (left); 10,5x9,5x8	Synovial sarcoma	G2 (3/1/1); pT2b, pNX ◊	Increasing tumescence in pregnancy	Spontaneous abortion; weight unknown; patient could not remember week of abortion and did not want to know the sex of the fetus; dead	Resection	[c]
VII	Pain and growing mass both noticed in the 30th week of pregnancy	2nd in 2009	Thigh dorsal (right); 10x9x5	Liposarcoma	G2; pT2a Δ	Increasing tumor volume in pregnancy	vaginal delvery; 3200 g; 41th week; female; healthy; –	Resection	4 months postpartum
VIII	Pain, tumescence[c]	3rd in 2003	Foot (right); several sarcoma focuses	Fibrosarcoma	G1; pT2b	Increasing pain and tumescence until 3rd treatment	vaginal delivery; 3500 g; 40th week; male; 10	3 times amputation	gestational age of 24, 27 and 28 weeks

[a]Patient could only provide range of time
[b]On the recommendation of the FNCLCC clear cell sarcomas should not be graded
[c]Unable to retrieve exact time
◊UICC TMN Staging 6TH edition 2002
ΔUICC TMN Staging 7TH edition 2010

Table 2 Tumor history

	Age at pregnancy	First symptom/sign: gestational age in weeks	Gestational age at delivery (weeks)	Definite Diagnosis: time of successful biopsy	Time between symptoms and diagnosis	Number of doctors visited	Misdiagnosis	Imaging in pregnancy	Biopsy in pregnancy (gestational age in weeks)
I	29	27-32[a]	36	8 months postpartum	10 months	10	Inflammation; PVNS[b]	No	Yes (34)
II	29	39	40	11 months postpartum	12 months (354 days)	3	Osteomyelitis	No	No
III	26	33	40	6 months postpartum	8 months (298 days)	5	Infectious bursal disease	No	Yes (35)
IV	30	32-35[a]	38	4 months postpartum	6 months	2		No	No
V	40	34	41	4 months postpartum	6 months (166 days)	3	Femoral head necrosis	No	No
VI	26	14-18[a]	-	[c]	[c]	8	Inguinal hernia	[c]	[c]
VII	33	32	41	4 months postpartum	6 months (172 days)	2	Adipose tissue; tumescence	No	No
VIII	32	[c]	40	gestational age of 24 weeks	[c]	4	Lymphedema, Giant cell tumor	MRI, US	Yes (24)

[a]Patient could only provide range of time
[b]Pigmented villonodular synovitis
[c]Unable to retrieve exact time

3.2 ± 1.9 doctors until they were diagnosed correctly. No statistically significant difference compared to the pregnant patients (p = 0.183) could be detected in this regard. The time from the first consultation to the correct diagnosis accounted for 6.1 ± 1.9 months for controls. Therefore the delay in diagnosis was significantly higher for pregnant patients (p = 0.039) compared to non- pregnant controls. The mean maximum tumor size in control patients was 7.7 ± 2.9 cm. The tumor size of pregnant patients was significantly larger (p = 0.042) compared to the size of tumors in control patients.

Therapy

In no case radio- or chemotherapy was administered during the course of pregnancy. In two cases neoadjuvant treatment was performed after delivery; one patient received chemotherapy, and the second was treated with radiation therapy. One patient had to be amputated (fibrosarcoma) three times consecutively during week 22, 25 and 26 of pregnancy, because the histology reports showed only marginal or intralesional resection twice. The patient was able to give birth to a healthy infant, who is eight years old and in good health today.

The remaining seven patients underwent surgery after delivery. A limb salvage procedure was performed on five patients. One patient had to be treated with hemipelvectomy (osteosarcoma, chondrobl.), one patient was treated with a rotationplasty (clear cell sarcoma, soft tissue). Several patients received adjuvant therapy after delivery and surgery, three of them were treated with radiation therapy and another three received chemotherapy (for details regarding therapy see Table 3). Within the control group a limb salvage procedure was performed in 15 cases and a rotationplasty was performed in one patient.

Outcome

At the time the study was conducted, seven out of eight patients were alive. These seven patients were without evidence of disease. The other patient had been referred to our clinic at a very late stage and had already been suffering from metastases. She received adjuvant chemo- and radiotherapy and died of disease nine months post surgery.

The seven disease-free patients described their general health as good and normal. Five women delivered vaginally, caesarean section was performed in two cases and spontaneous abortion was reported in one case. On average the patients delivered in week 39, the delivery was considered on time in six cases, whereas one baby was born in week 36. At the time the study was conducted thirteen out of sixteen control patients were alive without evidence of disease, one was suffering from recurrence and two from recurrence with metastases. According to Fisher's test there was no significant difference detected between seven patients (out of eight) without evidence of disease in the patient group compared to 13 control patients (out of sixteen) without evidence of disease.

Discussion

The occurrence of a malignancy during the course of pregnancy is certainly rare but devastating. The situation is very uncommon for medical professionals and it is a challenge to make the right decisions at the right time. Literature concerning these issues is scarce. Our study adds to this body of research by presenting eight pregnant women with a malignancy during pregnancy.

Our results highlight the problem that a suspicious musculoskeletal mass during pregnancy presents a diagnostic challenge and often leads to misdiagnosis. Interpreting the various symptoms was challenging for the medical professionals. This is indicated by the fact that the period between the first consultation and the correct diagnosis was significantly longer for pregnant patients and by the fact that the tumors were significantly larger compared to non-pregnant controls. The literature reveals that the average delay in diagnosis of musculoskeletal tumors is four to six months [12, 13], this

Table 3 Therapy details

	Radio- or Chemotherapy in pregnancy	Neoadjuvant treatment	Surgical treatment	Adjuvant treatment
I	No	No	Marginal tumor resection after delivery	Radiotherapy
II	No	No	En-bloc Resection after delivery	Chemotherapy;
III	No	No	Rotationplasty after delivery	Chemotherapy; Radiotherapy
IV	No		En-bloc resection after delivery	Radiotherapy
V	No	Chemotherapy (febril neutropenia)	Hemipelvectomy after delivery	Chemotherapy
VI	No	No	Resection after delivery	Radiotherapy
VII	No	Radiotherapy	Resection after delivery	No
VIII	No	No	3 times amputation in pregnancy[a]	No

[a]surgery in week 24, 27 and 28 (gestational age in weeks)

shows the delay in diagnosis in our control group was in line with the data in the literature. In addition this also points out that diagnoses in our series of pregnant tumor patients were made comparably late (eight months diagnostic interval).

The tumor size in pregnant patients was significantly higher compared to controls in this study. Research has shown that the size of soft tissue tumors is related to survival and that the chance of cure is lowered by 3 % to 5 % per centimeter increase in size [14]. Recent studies from the United Kingdom reported a mean diameter of eight to ten cm for soft tissue sarcomas [15, 16], while a Scandinavian report found a mean size of seven cm and an Italian analysis stated a mean size of only six cm [17, 18]. Therefore the tumor size of tumor in our control group is in the range of the literature data and the tumor size of pregnant patients in this series is comparably high. All women except one survived although the diagnostic intervals seemed increased. Comparing pregnant patients with controls with Fisher's test concerning the number of patients without evidence of disease reveals no significant difference, however the low number of cases of this series could have led to a bias in this regard and the statistical analysis should not be overestimated.

We advise that in cases where the etiology of a growing tumor mass is not clear the patient should be referred to a tumor center for diagnosis and management. Given that there was a hesitancy to perform imaging during pregnancy in six of our eight cases we advise that imaging should be arranged, keeping in mind the information gained by the study versus the fetal risks of various exposures. Diagnosis including each imaging modality and management of musculoskeletal tumors is discussed in the following sections.

Diagnosis

Ultrasound

The prenatal use of ultrasound (US) imaging for fetus screening is well established [19]. New imaging techniques such as 3D US have become available in clinical practice and they are increasingly used for gynecological diagnostics [20]. Since this form of imaging has no side effects it is strongly recommended for the use in diagnostics of soft tissue masses during pregnancy.

Magnetic resonance imaging

Although magnetic resonance imaging (MRI) has been increasingly performed for gynecological issues in recent years (since there is no ionizing radiation exposure for the patients) the safety of fetal MRI has not been fully evaluated yet [11]. Chen et al. suggest that the use of MRI in the first trimester should be considered, but is still preferable to any imaging involving ionizing radiation [21]. Shellock et al. state that MRI may be performed (in the first trimester also) if the procedure has the potential to improve the care of the mother or fetus [22]. In the 'American College of Radiology Guidance Document for Safe MR Practices: 2007' Kanal et al. state that if a MRI scan is necessary during pregnancy and the risk-benefit ratio is acceptable, it can be performed at any stage of pregnancy [11].

MRI contrast agents should not be routinely administered to pregnant women [23]. Since gadolinium-based MRI contrast agents diffuse across the placental barrier into the fetal circulation, gadolinium is contraindicated during pregnancy [21].

Radiation exposure: X-ray and Computed Tomography

Radiation exposure should be avoided during the course of pregnancy whenever possible. It should be taken into account that exposure dosages vary with different image procedures and the type of radiation beam. Radiation shielding is essential, but very often there still remains a considerable exposure, which arises from scattered radiation within the patient [11]. The expected fetal dose has to be calculated or should be simulated in a humanoid phantom model as reported by Mazonakis et al. in every case with uncertain risk for the embryo [24]. Regarding possible negative effects the risk of spontaneous abortion is highest in the first two weeks [21]. At weeks 2–7 mainly gross malformations and growth restriction were found [25].

At weeks 8–15 the fetus is most vulnerable for mental retardation and is still at risk for gross malformations and growth restriction [26]. The risks of mental retardation and growth restriction remain at weeks 16–25.

The concentration of free iodine in more recently used water-soluble contrast media is relatively low, but it remains unclear to which extent it crosses the placenta. Therefore, the application of iodinated contrast media should only be performed in cases where the application is essential for the particular radiographic procedure because of the risk of neonatal hypothyroidism [11].

Nuclear medicine

Most diagnostic nuclear medicine procedures seem applicable during pregnancy [27]. Kal and Struikmans state that short-lived radionuclides such as technetium-99 m would not expose the fetus to large doses of radiation and the dose the fetus is exposed to should be lower than 0.01 gray (Gy) [27]. However, the application of diagnostic nuclear medicine procedures should still be deliberated and the procedures should only be used in cases in which the results would change treatment management during pregnancy. Their application should be discussed multidisciplinary and usually postponed to after the delivery.

Biopsy

Grimer et al. stated in their review about diagnosing musculoskeletal tumors during pregnancy that the patients should always be referred to a specialist center prior to biopsy and that the biopsy should be carried out in the center where treatment is eventually going to be performed [28]. We have to endorse this recommendation with regard to the literature and this series.

Management

Once diagnosed, a musculoskeletal sarcoma requires careful analysis and consideration whether and to which extent treatment is acceptable for both - mother and fetus.

Surgical treatment during pregnancy

Only a few case series reporting on surgical treatment of musculoskeletal tumors during pregnancy have been published so far [8–10]. Anesthesia of pregnant women needs a certain preoperative assessment. It is necessary to pay attention to the fetal and maternal physiology and to select appropriate anesthetic techniques and supportive postoperative care is crucial [11]. Pregnancy causes large hemodynamic changes, which increase the cardiac workload. Furthermore there are vascular changes together with an accumulation of complications caused by blood clotting and hemorrhage [29]. These changes during pregnancy have to be taken into account before any surgical treatment. Multidisciplinary prearrangement of anesthesiologists, surgeons and obstetricians is essential for a successful management [30]. Obstetric surgery during pregnancy can be performed relatively safely provided that an anesthesiologist familiar with the physiologic changes of pregnancy is present. After 20 weeks of gestation positioning of the patient with left lateral uterine displacement is suggested to avoid aorto-caval compression by the growing uterus during surgery [31]. Intraoperative fetal monitoring is recommended for procedures at or after 24 weeks of gestation, otherwise fetal viability should be documented before and after the procedure [31].

Radiotherapy and Chemotherapy

According to Kal and Struikmans most cancers can be treated with radiotherapy even during pregnancy [27]. Pelvic cancers should not be treated with radiotherapy during pregnancy, because of the proximity to the fetus [27]. The dose for the fetus depends on the particular procedure, the radiotherapy treatment hardware and the shielding [27, 32]. In cases where radiotherapy promises a significantly better maternal prognosis we suggest a multidisciplinary panel discussion. This has to focus on minimizing the risks for the fetus by taking the recent literature on risk minimization and dose reduction into account [32–34].

According to the literature, systemic chemotherapy should not be electively started during the first trimester but several chemotherapeutic agents seem applicable during the second or third trimester [35, 36]. It needs to be stressed that chemotherapy is a treatment that requires a multidisciplinary approach and it should only be administered if absolutely necessary and with taking current literature into account [6, 31, 35, 37, 38].

Limitations of the study

Several limitations could not be foreclosed, including a potential inherent selection bias due to the retrospective nature of the analysis. However, due to the absolute rareness of cases with coincidence of sarcoma and pregnancy, a prospective study is cumbersome. The collection of cases was limited to a single institution and was based on a relatively small number of cases, which may also have led to bias. Therefore the power of statistics is low and the statistical results should not be overestimated. Further limitations are the inhomogeneous follow-up and relying on the amnestic annotations of pregnancies voluntarily offered by the patients. The hesitancy of some women to provide a history of elective pregnancy termination or early miscarriage could have led to an underestimation of the incidence of cases.

Conclusions

Diagnostic follow-up of pregnant women presenting with a growing or painful mass, which is suspected to be a musculoskeletal tumor, should be performed at a specialized tumor center. We recommend a multidisciplinary approach and discussing all possible consequences for mother and child intensively in accordance with the available literature.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LKP and GG contributed to study design, data collection and drafted the manuscript. AT and FP contributed to study design, data collection and analysis. HR, RvER, RB and CK contributed to study design analysis and manuscript review. All authors read and approved the final manuscript.

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