Melanoma during Pregnancy: A Report of 60 Pregnancies Complicated by Melanoma.

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Abstract

Objective: The management of melanoma in pregnancy is challenging since maternal benefits and fetal risks need to be balanced. Here, we present an overview of maternal and fetal outcome, clinical characteristics and treatment modalities, providing recommendations for clinical practice.

Methods: From the 'International Network on Cancer, Infertility and Pregnancy' database, pregnant patients with melanoma were identified and analysed.

Results: Sixty pregnancies were eligible for analysis. Fifty percent of the patients presented with advanced melanoma during pregnancy (14 stage III, 16 stage IV), and 25% were diagnosed with recurrent melanoma. Surgery was the main therapy during pregnancy. Only four patients with advanced melanoma were treated during pregnancy with systemic- (n = 1) or radiotherapy (n = 3). Premature delivery was observed in 18% of the ongoing pregnancies, all of which were induced and 78% of which involved patients with advanced melanoma. Thirty-nine percent of the patients died within five years , all had been diagnosed with stage III or IV disease during pregnancy.

Conclusion: Melanoma can present in a more advanced stage during pregnancy. New systemic therapies may be beneficial for patients with metastatic melanoma but may not be pregnancy compatible. In these patients, (preterm) induction of labour need to be discussed, despite the short and long term negative effects of preterm birth on the child.

Keywords: cancer, pregnancy, melanoma, preterm.

Introduction

Cancer in pregnancy is uncommon with an incidence of one in 1000 to 2000 pregnancies. The most common types of malignancies in pregnancy are those affecting young women of childbearing age, such as breast cancer (36%), haematological malignancies (16%), cervical cancer (11%) and melanoma (6%).[1–3] For melanoma, the overall incidence has been rising over the last couple of years, including in premenopausal women. For these women, the incidence of melanoma is 6 per 1000 women yearly. This, together with tendency for women to delay childbearing is suggested to be the main reason for the increasing incidence of pregnancy-associated melanoma.[4,5]

The incidence of stage I and II melanoma in young adults is reported to be 95% with a 5 year survival of 93%.[6–9] In the pregnant population, a concerning delay in diagnosis has been documented possibly due to the tendency for both patients and health workers to address changes in pigmentation as only physiologic due to pregnancy. This may possibly result in a higher stage of disease at diagnosis.[10]

Published case reports and small case-series raise concerns about the poor prognosis of pregnant compared to non-pregnant women with melanoma.[11–13] Other recent studies have shown no significant difference between the prognosis of pregnant and non-pregnant melanoma patients when corrected for age and stage.[14–17] These studies were conducted before the introduction of newer immuno- and targeted therapies. Since these newer therapies are possibly teratogenic, it is not advised to administer these agents in pregnant patients.[18–20] Theoretically, this may lead to a less favourable outcome for pregnant melanoma patients compared to the non-pregnant population.

The literature on the management of melanoma during pregnancy and the impact on fetal outcome is scarce and to date does not include current treatment options such as immunotherapy and targeted therapy. The present study will describe the incidence of melanoma in our database, the demographic and clinical characteristics of the identified patients and the treatment modalities used.

Recommendations for clinical practice will be provided after analysing both obstetric and maternal outcomes.

Methods

Study design

This study was a European observational cohort study. Cases were selected from the database of the 'International Network on Cancer, Infertility and Pregnancy' (INCIP) initiative (ClinicalTrials.gov, NCT00330447). The INCIP started in 2005 with a registration study on pregnant patients with any type of cancer and contains, at the moment of analysis, information reported by 70 healthcare workers from 62 medical centres in 25 countries.[21] Reporting of patients occurs on a voluntary basis by doctors affiliated to the INCIP, all of whom work in specialised hospitals where patients with cancer during pregnancy are treated.

Selection criteria and data collection

Patients diagnosed with histologically confirmed invasive melanoma during pregnancy were eligible. Patients diagnosed postpartum were excluded from this study. Patients were staged according AJCC guidelines; pregnant patients with recurrent melanoma restaged at recurrence. Data on demographics, symptoms, diagnostic and therapeutic interventions and outcome were collected. INCIP members were requested to update the clinical data of their patients before the start of this study.

Results

Incidence

In August 2016, the INCIP database contained 1406 patients of which 68 patients were classified as having a melanoma. Nine patients were excluded from this analysis because they were diagnosed postpartum (n=7), had a melanoma in situ (n=1) or were diagnosed more than 40 years ago (n=1). Of the

59 remaining patients, 44 had primary melanoma and 16 developed recurrent melanoma during pregnancy. One patient was diagnosed with recurrent stage IV melanoma in her second pregnancy after being diagnosed with stage III melanoma in her first pregnancy. Therefore, information on 60 pregnancies was available.

Demographic and clinical characteristics

Patients were diagnosed between 1994 and 2015 (55 patients after the year 2000) in five countries (The Netherlands (n=37), Belgium (n=15), Czech Republic (n=2), Denmark (n=2), Italy (n=2) and Poland (n=1)). Ninety-seven percent was Caucasian. Five women reported a positive family history for melanoma. Information on patient's naevi profile was not available, and the presence of dysplastic nevus syndrome was not reported. Patient characteristics of age, gestational age (GA) and parity at diagnosis are shown in Table 1. Aside from two patients who became pregnant during treatment, all women were pregnant at the time of diagnosis . During pregnancy, 50% of patients presented with regional (n = 14) and metastatic disease (n = 16). Half of these patients had recurrent melanoma during pregnancy (n = 15, see Table 2). The most common symptom at presentation was the changed appearance of a nevus (n = 45), followed by an enlarged lymph node (n = 9), complaints of metastases (n = 5) or increased tumor marker S100 (n=1).

In the patients diagnosed during pregnancy (n = 58) diagnostic excision of the nevus or biopsy of the lymph node was performed in all but two patients, the latter presented with metastatic disease on imaging. Additional diagnostic examinations during pregnancy were non-obstetrical ultrasound (US) (n = 17), chest x-ray (n = 9), magnetic resonance imaging (MRI) (n = 6), computed tomography (CT) scan including the abdomen (n = 3), positron emission tomography (PET) scan (n = 2) and mammography (n = 1, see Table 1). The two patients who underwent a PET/CT scan, terminated their pregnancy shortly afterwards.

Treatment

Surgery during pregnancy was performed in 52 patients. Excisional biopsy was performed in 46 pregnant patients, of which 27 additionally underwent a re-excision during pregnancy. Sentinel node procedure (SNP) was performed in 11 pregnant patients followed by lymph node dissection (LND) in 5 during pregnancy. Postpartum seven additional patients underwent a SNP followed by a LND in two patients. There was no difference in time interval between the excision and SNP performed during pregnancy and the SNPs performed postpartum. Primary LND, without previous SNP, was performed in nine patients, of which five (56%) were pregnant at that time. Of these nine patients, three only reported symptoms of a dysplastic nevus, while the other six had enlarged lymph nodes at the time of diagnosis. Although 27% of the patients had distant metastases during pregnancy, 56% of these patients still underwent surgery during pregnancy.

Only one patient with stage IV recurrent metastatic melanoma received systemic therapy during pregnancy; two cycles of dacarbazine/cisplatin at a GA of 19 and 22 weeks and one cycle of cisplatin/vinblastine at 27 weeks. Details concerning the decisions of whether or not to start systemic therapy in stage IV disease was not available. One patient terminated pregnancy at a gestational age (GA) of 19 weeks after starting treatment with a BRAF inhibitor (vemurafenib). Three other patients were treated with radiotherapy during pregnancy. One patient received plaque brachytherapy with iodine-125 for ocular melanoma and two with stage III and IV disease received radiotherapy of the axilla, all within their second trimester. Estimated fetal dose of radiation (EFD) was reported to be negligible in all three cases.

Obstetrical outcome

Obstetrical characteristics and outcomes were available for 53 pregnancies (Table 3). Of all ongoing pregnancies (n = 49), median GA at delivery was $39^{1/7}$ weeks (range $31^{1/7}$ to $42^{3/7}$). Prematurity was observed in 18% (n = 9) of the pregnancies. When stratified by stage, the rate of premature births was the highest in pregnant patients with stage III disease (45%), followed by stage IV (33%) and II (22%). No premature birth was observed in pregnant patients with stage I disease. Seven of the nine cases of preterm birth were iatrogenic, and in two pregnancies the start of (spontaneous or induction) labour was unknown. In one premature delivery, labour was induced on mothers request because of fear for placental metastases. The six other pregnancies ended with an elective CS because of maternal deterioration (n = 3), fetal distress (n = 2) or therapy planning (n = 1). For the term pregnancies 52% were delivered by a caesarean or assisted vaginal delivery. Ten term pregnancies were induced for obstetrical reasons (n = 4), maternal deterioration (n =3), therapy planning (n = 2) and patients wish due to the psychological burden of the melanoma (n = 1). Eleven elective CS were performed for obstetrical and oncological reasons.

Three patients, one stage I and two stage IV disease, opted to terminate the pregnancy before 20 weeks of gestation. One because of major fetal malformations (diagnosed before start of therapy), one to enable administration of targeted therapy and one because of poor maternal prognosis. One patient and her fetus died suddenly during pregnancy at 29 weeks GA after being diagnosed with stage IV melanoma with widespread metastases suspected in the uterus and placenta on MRI. No autopsy was performed. Histopathological examinations did not show placental metastasis and fetal metastases were not diagnosed after clinical examination of the neonate.

Fetal and maternal outcome

All remaining ongoing pregnancies resulted in delivery of a healthy newborn (n=56). Congenital abnormalities were not observed and neonatal deaths did not occur including the children exposed to

systemic therapy and radiation. The mean birthweight was 3377 grams (range 1850 – 4230). Birthweights of all but two children were within the 10th and 90th percentile. Three term neonates, were admitted for an infection, Rhesus D haemolytic disease of the new-born and respiratory insufficiency. Maternal follow-up (FU) was available for 55 patients with a median FU of 2.5 years (range 2 weeks – 16 years). Maternal survival after melanoma during pregnancy stratified by stage of disease can be seen in Figure 1. Overall, 5 year survival was 61%, but death only occurred in patients with stage III and IV disease.

Discussion

This study analysed the oncological and obstetrical outcome of 59 pregnant patients with melanoma and their 60 pregnancies. The incidence of advanced stage disease was high in our study population with half of the women having stage III (23%) or IV (27%) disease at diagnosis. Surgery was performed during pregnancy even in patients with distant metastases and 38% of SNP were postponed until after delivery. Half of the LNDs were performed without previous SNP. Only one patient received chemotherapy during pregnancy. Preterm delivery occurred mainly in advanced stage disease (III and IV) and was induced in all cases. As expected, patients with stage III and IV disease had a higher 5-year mortality rate than those with stage I and II disease during pregnancy.

In the literature, the incidence of stage III and IV melanoma in young adults is reported to be 1-5%.[6–8] A possible explanation for the relatively high incidence of advanced disease in our study population could be delay in diagnosis in pregnancy. Due to hormonal changes during pregnancy hyperpigmentation and morphologic changes occur in melanocytic naevi contributing to a delay in the diagnosis of melanoma. Melanocytic naevi during pregnancy have been studied with different techniques and changes in colour and size were not found to be a normal consequence of pregnancy.[22–29] Naevi with a changing morphology during pregnancy need to be considered a

pathological symptom as in the non-pregnant population. Another possible explanation for the high incidence of advanced stages in our study, could be the under reportage of low stage disease in pregnant patients.

The management of pregnant patients with melanoma should not differ from non-pregnant patients in order to achieve similar outcomes. In our study population, patients were primarily treated with surgery during pregnancy. Currently, surgical removal of a suspected melanocytic lesion with a 2 mm margins and re-excision with 1 cm (Breslow thickness ≤ 2 mm) or 2 cm margin (Breslow thickness > 2 mm) is the keystone in treatment of localized melanoma. Surgery in pregnancy is proven to be feasible. For staging and estimation of prognosis, examination of regional lymph nodes with a SNP should be discussed with patients with melanoma stage IB and higher.[9,24,30,31] When using a radionuclide with a short half-life, such as 99-Techneticum nanocolloid, the estimated fetal radiation exposure of a SNP during pregnancy is <5 mGy. No adverse effects on the fetus have been described after SNP in pregnancy.[31–33] Since performing a SNP (and additional LND) has not been proven beneficial for survival of melanoma performing these procedures should be decided on an individual basis. In this report, a third of the SNPs performed were postponed until after delivery and 53% refrained from this staging procedure.

Until recently, chemotherapy was the only treatment modality for metastatic melanoma with low response rates and no significant effect on survival.[34] In the last four years, treatment for metastatic melanoma has changed dramatically with the introduction of targeted- and immunotherapy. These therapies are currently the initial treatment of choice, each with encouraging results.[35,36] The effect of these therapies on the unborn child in pregnant women has not yet been established and administration of these medications is not recommended during pregnancy. The application of the BRAF V600 inhibitor vemurafenib has only been reported once in pregnancy and fetal growth declined progressively resulting in premature caesarean section for fetal distress. No malformations were

reported.[18] The case exposed here to BRAF inhibitor (vemurafenib) elected termination of pregnancy. The anti-CTLA-4 antibody ipilimumab (IgG1) crosses the placenta and an increased incidence of miscarriages, stillbirths, premature births, neonatal death and urogenital tract malformations was shown in monkeys.[19] For the newer anti-PD-1 antibodies nivolumab and pembrolizumab (IgG4) the effects on pregnancy have not been described in humans, but in mice blockade of the PD1/PDL1 pathway resulted in fetal loss. Since PD1/PDL1 is essential in downregulating T cell function necessary for maintaining tolerance of the pregnancy, a negative effect on human pregnancy may be expected when using anti-PD-1 antibodies during pregnancy.[20] Of our 16 patients with distant metastasis during pregnancy, only ten patients were treated with systemic or radiotherapy, including 4 treated during pregnancy: systemic- therapy (n = 1) or radiotherapy (n = 3). Postpartum therapy consisted of chemotherapy in 9 cases , and targeted therapy in 3, of which two patients received both. Presumably, chemotherapy was not given during pregnancy in these women because of the minimal effect on survival and the fear for possible negative effects on the fetus. In the seven patients who did not receive any systemic therapy, not applying these therapies during or after pregnancy can be considered as substandard care. Of the patients with distant metastases, 13 (81%) were diagnosed before the introduction of targeted therapies, and chemotherapy was the standard treatment. Two of the patients receiving targeted therapy postpartum were treated in an experimental setting before de European FDA approval of vemurafenib and ipilimumab in 2012.

In women diagnosed with cancer during pregnancy, preterm birth occurs more often, both spontaneously and induced.[2] In our study group 18% of the patients delivered preterm and in all patients, labour was induced. Preterm birth has more impact on the overall and neurological development of the newborn than chemo- and radiotherapy.[37] For many tumour types, chemotherapy is started during pregnancy in order to postpone delivery and increase gestational age. In the population with advanced melanoma (78% of the preterm births in our population), the discussion

of whether or not to induce a preterm birth has become more relevant over the last couple of years with the promising results of immuno- and targeted therapies, since these therapies are not compatible with pregnancy. The decision to induce a preterm delivery or terminate a pregnancy in order to start maternal targeted or immunotherapy for this specific group of patients should be carried out by a team of melanoma experts, obstetricians and medical oncologists.

Level A evidence-based guidelines for the treatment of melanoma during pregnancy do not exist due to the lack of randomized controlled trials. Eventhough this study is one of the largest case-series not only focussing on maternal outcome but also on diagnosis, treatment and obstetrical outcome, we are aware that our number of patients is small. We cannot guarantee that our study includes all pregnant melanoma patients, since patients were selected retrospectively from the INCIP database and it is therefore possible that case selection bias may have occurred. Since registration of these cases is voluntary the completeness of the database cannot be guaranteed. However, it is unlikely that this selection bias has influenced the stage at diagnosis since all participating hospitals have registered all their cases and not just selected the cases with a poorer outcome. It is possible that thin melanomas with excellent prognosis, were surgically treated in general hospitals and not referred to tertiary centres.

Nonetheless, our data on clinical characteristics, interventions during pregnancy, obstetrical and maternal outcome adds important information and is the first case-series that addresses the issue of premature birth and systemic therapies in pregnant women with metastatic melanoma.

In conclusion, melanoma can present in a more advanced stage during pregnancy, possibly because of a delay in diagnosis. Standard surgical therapy in pregnant patients with melanoma, including sentinel node biopsies, is feasible for patients with stage I-III without harming the fetus. Preterm delivery should be avoided when possible in patients without advanced stages. In women with metastatic disease who are likely to benefit from immuno- and/or targeted therapy, preterm induction of labour may be needed, despite the short and long term negative effects of preterm birth on the child.

The oncological and obstetrical management should be discussed in a multidisciplinary setting, where balancing maternal and fetal chances is the challenge.

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Details of ethics approval

Ethical approval was obtained from all participating centres.

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Table 1. Patient characteristics

Characteristic	Median (range)
Age in years	33 (21-44)
Parity	1 (0-3)
GA at diagnosis in weeks	21 (2-39)
Primary vs recurrent melanoma, n (%)	n (%)
- Primary	44 (73)
- Recurrent	16 (27)
Diagnostic examinations during pregnancy, n (%):	n (%)
Excision/biopsy	56 (93)
Ultrasound	17 (28)
X-ray chest/mammography	10 (17)
MRI	6 (10)
CT scan	1 (2)
PET/CT scan	2 (3)

GA; gestational age, *MRI;* Magnetic Resonance Imaging, *CT;* Computed tomography, *PET;* positron emission tomography.

Table 2. Stage of disease during pregnancy in primary and recurrent melanoma, according to the American Joint Committee on Cancer (AJCC).

AJCC stage, n (%):	Primary melanoma	Recurrent melanoma
- I	19 (32)	0 (0)
- II	10 (17)	1 (2)
- III	11 (18)	3 (5)
- IV	4 (7)	12 (20)

Table 3. Obstetrical outcome

Pregnancy termination	1 IUD/3 TOP
GA at delivery, median (range)	$39^{1/7}$ ($31^{1/7}$ - $42^{3/7}$)
Prematurity, n (%)	9 (100)
- Stage I	0 (0)
- Stage II	2 (22)
- Stage III	4 (45)
- Stage IV	3 (33)
Induced deliveries, n (%)[2]	28 (57)
Birth weight, grams (range)[3]	3377 (1850 – 4230)

IUD; intra-uterine death, *TOP;* termination of pregnancy, *GA;* gestational age. [2]Of all ongoing pregnancies. [3]data available for 55% of neonates.

Figure 1. Maternal outcome stratified by American Joint Committee on Cancer (AJCC) during pregnancy.