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CHAPTER 9

Recurrent melanoma after pregnancy and assisted reproductive technology

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ABSTRACT

Introduction

Melanoma is one of the most common cancers in fertile women. The effect of pregnancy and assisted reproductive technology (ART) on the recurrence of melanoma is still unclear. The aim of this study is to evaluate the incidence of recurrence of melanoma in pregnancy after spontaneous conception or after using ART.

Patients and methods

This study was a single centre questionnaire study among fertile women with a history of invasive melanoma. Questions concerned general health, primary tumour characteristics, development of recurrent melanoma, use of ART and occurrence of pregnancies.

Results

A total of 354 (49%) questionnaires were available for analyses, 309 from living women and 45 of relatives of diseased women. The majority of women (n=218, 63%) had stage I primary disease. In total, 135 women with a history of melanoma (38%) became pregnant after their melanoma diagnosis. Only 17 women (5%) conceived after using ART. There was no difference in recurrence rate between women who had ever been pregnant (before or after the diagnosis of melanoma) and those who had never been pregnant (37% vs 35%, p=0.775). In the small group of women who conceived after ART, the recurrence rate was 30% (n= 5).

Conclusion

Pregnancy did not increase the risk of recurrent melanoma. The group of women conceiving after ART was too small to assess a relation. Registration of these women, their oncologic follow-up and possible fertility treatments, will provide more information on the relations between ART and recurrent melanoma in the future which is of importance for preconceptional counselling.

INTRODUCTION

In the Netherlands, about 2700 women are diagnosed with melanoma each year and 24% of these women are between the age of 18 and 40 years.[1] This makes melanoma one of the most common types of cancer among fertile women.

The skin is a hormone sensitive organ and has many estrogen receptors.[2] Estrogens have protective and beneficial effects on the skin, and play a role in skin pigmentation. Therefore, hyperpigmentation can occure during pregnancy and in women taking exogenous hormones like oral contraceptives and hormonal replacement therapies.[2,3] The exact effect of estrogen on the incidence, progression and recurrence of melanoma is still not completely clear and data are conflicting. While some authors found an association between oral contraceptives (OC) or hormonal replacement therapy (HRT)[4,5] and melanoma, others did not.[6,7] Furthermore, pregnant women with melanoma and thus high estrogen levels, seem not to have a worse outcome compared to non-pregnant women with a melanoma when matched for stage and other prognostic factors.[8-10] However, the occurrence of stage III and IV disease has been reported in the pregnant melanoma patients[11] and an association between estrogen receptors in melanomas and poor prognosis has been described.[2] Another theory could be that at the beginning of pregnancy, adjustment of the immune system of the mother are made, necessary to prevent rejection of the fetus which could also play a role in the high stage disease in pregnancy.[12,13]

Women undergoing assisted reproductive technology (ART) are exposed to high doses of estrogens, as a response to exogenous gonadotrophins. Stewart et al.[14] reported an association between in-vitro fertilisation (IVF), birth and melanoma. They found no association between invasive melanoma and IVF treatment when the treatment was not followed by an ongoing pregnancy. However, they did find an increased risk (Hazard Ratio [HR] 3.61; Confidential Interval [CI] 1.79-7.26) for invasive melanoma in women who gave birth after IVF treatment compared with women who remained nulliparous.[14] In this study the causal relationship between melanoma and ART/pregnancy was not investigated and there was no data on the recurrence rate of melanomas. No evidence-based guidelines are yet available to advice women on safe use of ART after treatment for melanoma. Caretakers, however, will be confronted with the question whether pregnancy is safe after melanoma treatment.

With this study, we aim to evaluate the incidence of ART and pregnancies in women with a history of melanoma and to calculate a sample size necessary to investigate the influence of ART and pregnancy on the incidence of recurrent melanoma. In addition, we evaluated the medical advice given by caretakers in the absence of evidence and

guidelines. Finally, we investigated whether or not these women experienced uncertainty or anxiety concerning the safety of hormonal treatment and pregnancy.

METHODS

Study design

This study was a single centre pilot questionnaire study. Women were selected from the cancer registry of the Antoni van Leeuwenhoek (AVL), The Netherlands, which registers all patients diagnosed and/or treated for cancer at the AVL. Selected women from this database were crosslinked with the Netherlands Cancer Registry (NCR). Information on vital status and date of death is annually retrieved from the database of deceased persons of the Central Bureau of Genealogy and the municipal demography registries (GBA). The GBA was also used to obtain the current address or the address from their last registered partner or first degree relative(s). Ethical approval was obtained from the ethical committee of the AVL (NL52033.031.15/P16ART).

Data collection

Women diagnosed between 1994 and 2014 between 18 and 45 years of age with any stage of invasive melanoma were eligible for this study. Women with melanoma in situ and women with the inability to read and understand Dutch were excluded. Information on primary diagnosis and confirmed recurrent disease was collected from the database. The selected women were contacted by mail. The questionnaire contained questions about general health, primary tumour characteristics and, if applicable, the development of recurrent melanoma, use of ART, the occurrence of pregnancies and pregnancy outcome, the use of exogenous hormones, the received information or advices about hormones and pregnancy and women's own feelings about using hormones after their melanoma diagnosis. When women were deceased, last registered partner or first degree relative(s) were contacted for information upon missing data by a shortened questionnaire. For the relatives of deceased women, questions about exogenous hormone use except ART, were not included in the questionnaire. Data on diagnosis and recurrent melanoma was crosschecked with hospital files.

Definitions

Exogenous hormonal exposure included ART, HRT and OC. Pregnancy is considered as a state of increased endogenous hormonal exposure. Skin type was determined using the Fitzpatrick scale, based on a validated 8 point questionnaire on natural eye, hair and skin

colour, freckle pattern, burning reaction, tanning reaction, depth of tan and sensitivity of the face to sun exposure.[15]

Data analysis

Data was anonymized and entered into an Access database and analysed using Statistical Package for Social Sciences (SPSS Version 22). Analysis was mainly done by using descriptive statistics. Group comparison was done by using Chi-square tests. P-value was considered significant when below 0.05. It was not possible to calculate the sample size needed to answer our research questions prior to our study, due to lacking data on the pregnancy and ART rate in women with a history of melanoma. A clinical relevant difference in recurrence rate was defined as a 10% difference.

RESULTS

On July 7th, 2017, the database of the AVL contained 892 women that fulfilled the inclusion criteria. Information on whether or not these women were still alive and had a current address within the Netherlands was available for 727 women. The total response rate was 49% (n=354); 51% of the women (n=309) and 38% of the partners (n=45) of deceased women responded (Figure 1).

Demographic characteristics

Women were diagnosed with a median number of 14 women per year (interquartile range [IQR] 11 - 18). Baseline characteristics are shown in Table 1. Mean age at first diagnosis was 33 ± 6 years. Stage of disease was known for 97% of the women. The majority of women (n=218, 63%) were diagnosed with stage I disease. Forty-two women (12%) had a first degree relative with melanoma, 36 with a second degree relative (10%) and 35 with a other relative with melanoma (10%). Twenty-one women (6%) had multiple relatives with melanoma in their family but in only 15 women (6%) a familial DNA mutation was known. A history of smoking was present in 168 women (48%), but at the time of the questionnaire only 42 (12%) women were actively smoking. Most women had skin type II (n=145, 41%) and III (n=143, 40%). The median follow-up time was 11 years (IQR 6 - 17).

Pregnancy and assisted reproductive technology (ART)

Overall, 200 (59%) women had been pregnant before the first diagnosis of melanoma, and 182 of these 200 women (91%) had at least one ongoing pregnancy. Of all women, 135 (38%) became pregnant after the primary melanoma treatment and sixty-three (18%)

women never became pregnant. Thirty-five (10%) women underwent any form of ART, 18 (5%) before the primary diagnosis and 17 (5%) after the primary diagnosis. Twelve (71%) women were previously diagnosed with stage I disease, 2 (12%) had stage III disease, 2 (12%) had stage IV disease and for one women, stage of disease was unknown. Of those 17, five did not conceive after ART. The other 12 women had a total of 20 pregnancies, of which 15 were ongoing.

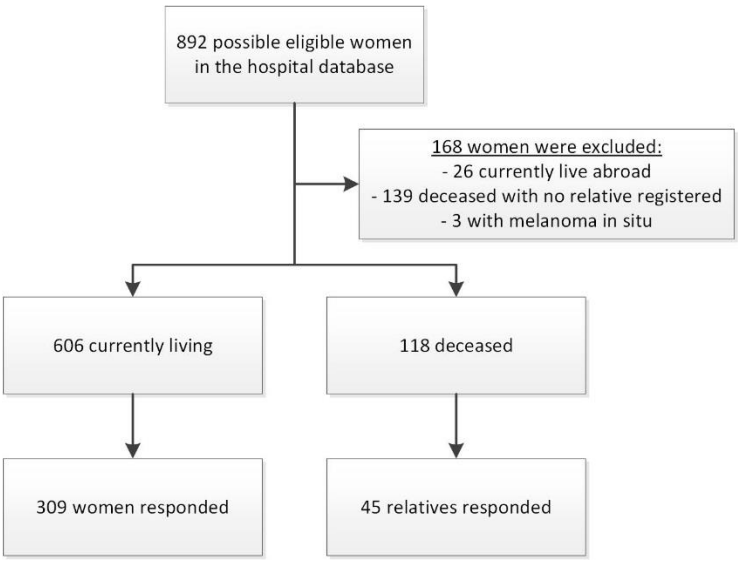

Figure 1. Inclusion flowchart

Recurrent melanoma

Recurrent disease occurred in 127 (36%) women, of which 28 (22%) presented with systemic disease. Women that conceived after the primary diagnosis had a comparable recurrence rate as women who did not conceive (38% vs 37%, p=0.821). There was no difference in recurrence rate between women who became pregnant after the first diagnosis and those who did not when stratified by stage of disease. This was also the case when only women with ongoing pregnancies were compared to women who did not conceive (34% vs 37%, p=0.628). There was no difference in recurrence rate between women who had ever been pregnant (before or after the diagnosis of melanoma) and those who had never been pregnant (37% vs 35%, p=0.775). In the group with ART after the primary diagnosis, five women (30%) had recurrent disease.

Table 1. Baseline characteristics.

	Mean	Standard deviation
Age at primary diagnosis	33	6
	No. of women	**% of women[a]**
Stage of disease at diagnosis		
I	218	63
II	63	18
III	56	16
IV	7	2
Missing	10	
Positive family history with melanoma	96	27
DNA mutation present	15	6
Smoking		
Never smoked	184	52
Ever smoked, but stopped	126	36
Currently smoking	42	12
Missing	2	
Skin type		
I	26	7
II	145	41
III	143	40
IV	40	11
V	-	
VI	-	
Parity at primary diagnosis		
nulliparous	156	44
1	59	17
2	96	27
≥ 3	27	8
Missing	16	

[a] Percentage is reported for all women with known outcome.

Advices and anxiety

The 309 women who were still alive at the time of the questionnaire, were asked if they had received any information about consequences of future pregnancy or ART from health care workers. Of all these women, 131 (44%) women had a pregnancy wish after their treatment for primary melanoma and 59 (45%) of these women requested counselling about the effect of pregnancy on the melanoma or vice versa. The advice to refrain from pregnancy because

of the possible negative effect of pregnancy, was given to 11 women (20%), 19 women (32%) were advised to wait on average 2-5 years before trying due to the increased risk of recurrence in the first years after diagnosis and 29 women (49%) were not discouraged to aim for a pregnancy. There were no reports of counselling for ART after a history of melanoma.

Only 72 women (23%) considered using exogenous hormones after the primary melanoma, of which 18 women (25%) reported being anxious for recurrent disease when starting exogenous hormone therapy (anxiety level ≥ 5 on a 10 point scale). For the women actually using hormonal therapies (n=56, 78%), only nine women (16%) reported being anxious about recurrent disease triggered by hormone use.

Sample size calculation

A clinical relevant difference in recurrence rate was defined as 10% difference. With a recurrence rate of 36%, a sample size of 766 women using ART would be needed (α=0.05, 1-β=0.80). With only 17/354 (5%) women undergoing ART after the diagnosis of melanoma almost 16000 women would be needed for an adequate study size.

DISCUSSION

This study reports on 354 women diagnosed with melanoma in their fertile years and the effect of pregnancy and ART on the recurrence rate. Overall, 36% percent of women had recurrent disease which was similar in women who had no pregnancy, conceived spontaneously or conceived after ART. The effect of ART however, has to be interpreted with caution, because only few women underwent ART after the primary diagnosis of melanoma (n=17, 5%).

Only two studies, published before 1990, reported on the effect of pregnancy on the recurrence rate of melanoma. The numbers of pregnant women in both studies were low, (n=23[16] and n=43[17] respectively) and both studies did not report a difference in recurrence rate.

Literature on the effect of ART on recurrence of melanoma is scarce. Most data published on ART and melanoma, assessed the relation between ART and risk of melanoma in general and not risk of recurrence specifically. Stewart et al.[11] found an increased risk (HR 3.61; CI 1.79-7.26) for invasive melanoma in women who gave birth after IVF treatment compared with women who remained nulliparous. IVF alone did not increase the risk. Luke et al.[18] did not find a significant increased short-term (5 years) risk for melanoma in women with ART therapy (standardized incidence ratios [SIRs] of 1.07 to

1.15). In other studies, no significant increase but a trend towards an increased risk for melanoma were observed.[19-22] These studies did not evaluate recurrence rate in women with a history of melanoma.

Forty-five percent of the women with a pregnancy wish after the primary melanoma diagnosis, requested preconceptional counselling about the possible interaction of pregnancy and melanoma and approximately half (49%) received a positive advice. Currently, no evidence based guidelines are available regarding preconceptional counseling. The Australian Cancer Network gives a consensus based advice to avoid pregnancy for two to five years which is based on the increased risk of recurrent disease in this period but states that every woman must be individually counseled, based on their own situation including stage of disease at diagnosis and maternal age.[23] No recommendations about the use of ART is given.

The number of women using ART after melanoma treatment was unknown before the present study. However, it was known that in women undergoing ART in the United States, a history of cancer is uncommon (717/113947, 0.6%).[18] The reason why this incidence is low in unclear. One of the aims of this study was to assess the number of women undergoing ART after primary melanoma to investigate the feasibility of a well powered national or international study. Based on the results of the present study, we calculated a sample size of 16000 women. With an average of 618 women between 20-44 years of age diagnosed with primary melanoma in the Netherlands per year[1], it would take over 25 years to include the required number of women, assuming that 100% of the women will participate. We had a 50% response rate, so many years more would be needed to complete a study like this. However, like in the rest of Europe, the number of women undergoing ART in the Netherlands has been increasing rapidly over the last years, from 4498 women in 2006 to 7908 women in 2013.[24,25] Thus, the number of women with a history of melanoma undergoing ART is also likely to increase, making the research question even more relevant. Although a potential study population will also become larger in the near future, a tremendous worldwide effort is still the only possibility to answer this research question in a shorter time period.

This study included all eligible women from a large specialized melanoma centre in the Netherlands. It is the largest study, specifically addressing the issue of recurrence of melanoma after pregnancy or ART. As with all questionnaire studies, our study is limited by the relatively low response rate, specifically in the group with diseased women. Since we describe a group of young women, it is likely that most of these deaths were melanoma related. Since death of melanoma is related with higher stage of disease at diagnosis and

recurrent disease it can be assumed that recurrence rates are higher. From these women we have no information on subsequent pregnancies or the use of ART. This could lead to an underestimation of the effect of pregnancy or ART on recurrence rate, at least for high stages. In addition, a recall bias could occur using questionnaire methodology. It is known that this bias occurs more often in studies with cancer patients.[26] However, most questions in our questionnaire were not about details of cancer treatment but about pregnancy and the attempt to get pregnant. This are life events, that women are unlikely to forget.[27,28] Also, verification of dates and recurrent disease was done using hospital records.

CONCULSION

We found no increased risk of pregnancy on recurrent melanoma. Data on the effect of ART after melanoma were limited by low patient numbers. However, questions from women about their risk of recurrent melanoma when trying to conceive, will be asked more frequently in the future and caretakers need to be informed about the current data by general guidelines in order to provide these women with the best information possible. Prospective registration of these women, their oncologic follow-up and possible fertility treatments, will provide more information on the relation between ART and recurrent melanoma in the future, which is of importance for preconceptional counselling.

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