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ABSTRACT

Background: Vertical transmission of maternal cancer cells to the child is extremely rare, but melanoma represents the most common culprit. The aim of this study is to determine individual risks for materno-fetal transmission of melanoma cells and to establish standardized procedures for pregnant melanoma patients and their offspring.
Patients and methods: In this retrospective multicenter study, data on women with stage III or IV melanoma that had been diagnosed before, during or up to 12 months after pregnancy, were analyzed for the occurrence of metastases in the placenta or the infant. In addition, a literature search for previously described materno-fetal transmission in case of maternal melanoma was conducted. A historical patient group was established from these cases and a statistical analysis was performed (SAS, $p < 0.05$ significant).
Results: In total, 67 children born to women with stage III or IV melanoma were included. No placental or infant metastases were detected in any of the cases. The additional literature search revealed 37 cases with placental metastases and 14 cases with infant metastases (6 of them overlapping). Of the affected children, 10 (71.43%) died from their disease. Maternal death shortly after birth seems to be an unfavorable factor for transmission to the infant.
Conclusion: The risk of materno-fetal transmission of maternal melanoma metastases seems to be much lower than anticipated based on former studies. However, thorough placental screening and systematic follow-up of the children resulting from pregnancies of high-risk melanoma patients should be performed.

1. Introduction

Cancer during pregnancy is a rare event with an occurrence rate of 1 per 1000 to 2000 gestations [1]. Melanoma is the fourth most common tumor type diagnosed in pregnancy after breast cancer, cervical cancer, and hematologic malignancies, and accounts for approximately 8% of all malignancies identified during gestation [2]. Given that the overall incidence of melanoma is increasing and women tend to delay childbearing, the number of pregnancy-associated melanoma (PAM) is likely to rise [3]. Although sparse, previously published data on the diagnosis, prognosis and treatment of PAM have focused primarily on the mother. However, the diagnosis of a PAM is clearly associated with great concern for the well-being of the child as well. Materno-fetal transmission of maternal malignancies to the offspring has been described for diverse cancer types, including leukemia, lymphoma, melanoma, and lung cancer [4]. It is estimated to affect one infant per 500,000 pregnant women with cancer [5]. Melanoma is known to be the tumor type with the highest risk of placental and fetal metastasis [6].

In 2019, a woman received the diagnosis of stage IV melanoma in the University Medical Center Mannheim shortly after giving birth and died 10 months after. Her son Claudius remained free from disease but was the reason for this study. Our aim is to estimate individual risks and to evaluate possible risk factors for transplacental transmission. This allows the development of standardized procedures for melanoma patients and their children to precisely inform the patient and assist the treating physicians in their decision-making.

2. Patients and methods

2.1. CLAUDIUS Study Group

In this retrospective multicenter study, 105 dermatology clinics and dermato-oncology practices in Germany and France were contacted. Of those, 29 centers were able to provide detailed clinical data sets of 63 melanoma patients covering a period from 2005 to 2021. Inclusion criteria consisted of advanced stage III or IV melanoma that had been diagnosed before, during or up to 12 months after pregnancy. The queried variables included detailed maternal and child characteristics, therapy, and the presence of placental and infant metastases. Placental metastasis was defined as gross or microscopic findings of maternal melanoma in any part of the placenta. Fetal or newborn involvement was defined as the development of maternal melanoma metastases in the infant without evidence of a primary tumor in the infant.

2.2. Comparison group: historical case reports

Since our collected data did not reveal a single case of metastasis in placental or fetal tissue, we tried to establish a historical comparison group by performing an extensive search of the literature for case reports with the occurrence of placental or fetal metastasis in case of maternal melanoma. Alexander et al. conducted a similar literature review covering the period from 1866 to 2002 and found 27 cases with placental or fetal involvement [6]. We reviewed the previously described cases again and performed a PubMed search from 1946 to 2021 with the search string [("Melanoma"[MeSH] OR Melanoma*[tiab] OR "skin cancer"[tiab]) AND (pregnancy[tiab] OR pregnant[tiab] OR placenta[tiab] OR placental[tiab] OR transplacental[tiab] OR fetal [tiab] OR fetus[tiab] OR foetus[tiab] OR "products of conception"[tiab] OR "vertical transmission"[tiab])]. 1627 articles were identified, and their titles and abstracts were screened for reports of metastasis of maternal melanoma to the placenta or fetus. Google Scholar was added as an alternative search engine, and various additional search strings were applied, as listed in Supplementary Table S1. Out of concern for missing untranslated articles, the search strings were also conducted in 7 other languages. Titles and abstracts were translated by the authors or the online translator DeepL. This search revealed 10 more reports of maternal melanoma spreading to the placenta, 3 more reports of both placental and infant involvement and 5 more reports of fetal metastases without recorded placental metastases. Added to the results of Alexander et al. [6], this leads to a total of 37 historical cases with placental metastasis and 14 historical cases with fetal metastasis (6 of them overlapping) described in the literature to date. An overview of all cases is shown in Supplementary Fig. S2. Since we intended to focus on child outcome, we used the 14 historical case reports in which mother-to-child transmission of melanoma metastases occurred as a high-risk comparison group to our own data.

2.3. Statistics

A statistical analysis was performed with SAS and Microsoft Excel

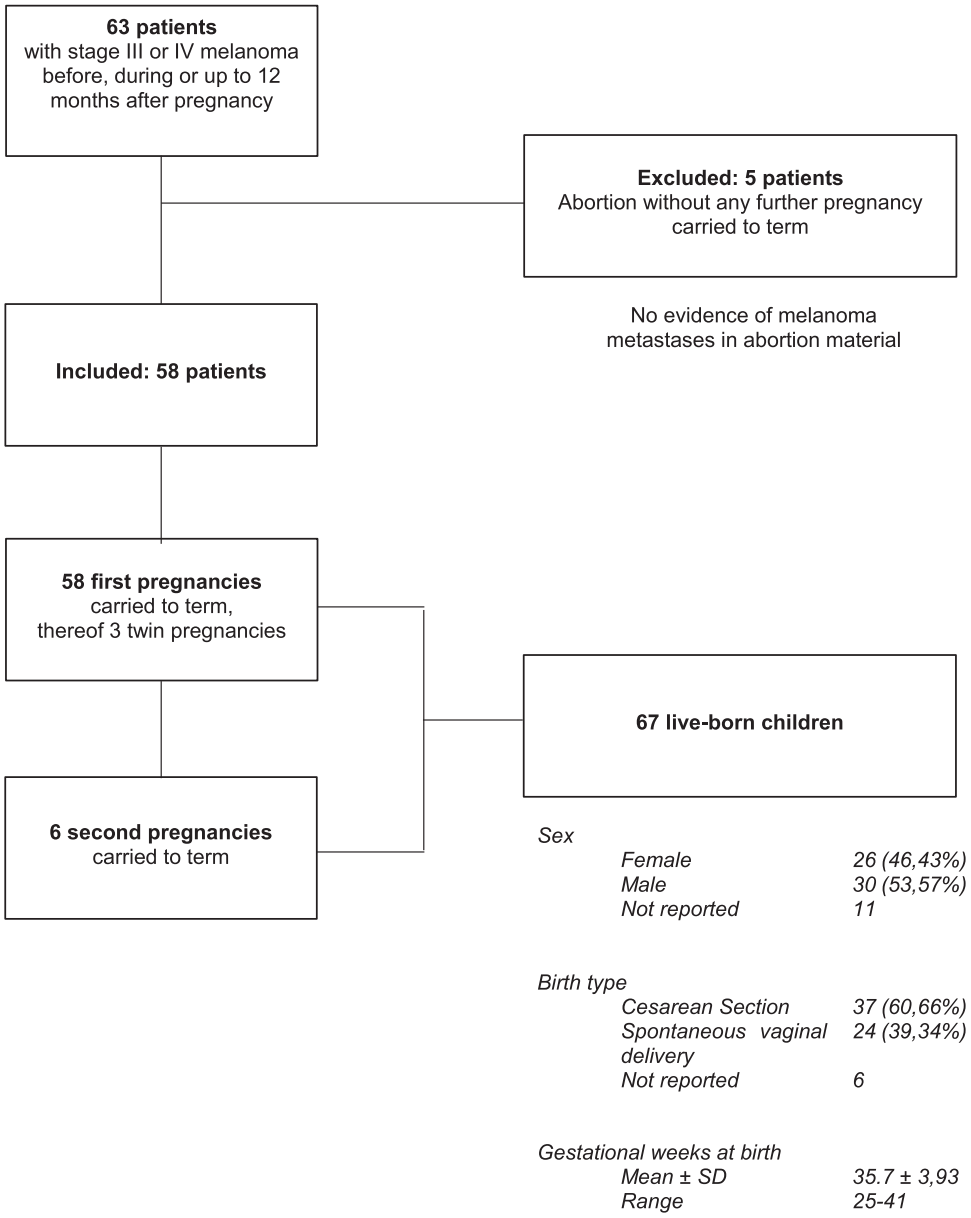

Fig. 1. Selection process of patient cases and infant characteristics of the CLAUDIUS Study Group.

(Microsoft Office 16). It compared 67 data sets from our retrospective multicenter study with all 14 cases from the historical comparison group, in which mother-to-child transmission of malignant melanoma occurred. In the new data, multiple pregnancies and twins were considered individually, as metastasis of only one of two twin siblings had already been described in the literature [7]. Abortions were not included in the comparison. Chi-square test or Fisher's exact test was applied to detect discrepancies regarding stage at diagnosis, maternal melanoma localization and mutation, infant sex, birth type and maternal and fetal outcome. To compare Breslow thickness, maternal age at birth, time of death after birth, and gestational age at birth, data was tested for normal distribution, and independent samples t-test or Mann-Whitney U Test was applied where appropriate. A p-value of < 0.05 was considered significant. Binomial tests were carried out and the Odd's Ratio was calculated to identify a clustering of the traits in affected children.

3. Results

3.1. CLAUDIUS Study Group

An overview of the selection process of patient cases is shown in Fig. 1. Data included 63 stage III or IV melanoma patients who became pregnant before (n = 21), during (n = 27) or up to 12 months (n = 15) after diagnosis. In the observed time frame, a total of 67 infants were born.

Eleven pregnancies were not carried to term (1 miscarriage and 10 abortions). Placenta screening was performed in 4 of those cases and showed no findings. In 6 women, another pregnancy in close temporal relation to melanoma disease was carried to term after the abortion, while the remaining 5 women were excluded from the analysis. Three twin pregnancies occurred, and 6 women had a second pregnancy in temporal relation to melanoma disease.

In the following consideration of maternal characteristics, the data of the first pregnancy carried to term was used and each of the 58 women was included only once. Maternal characteristics are shown in Table 1.

Table 1
Summary of maternal characteristics in the CLAUDIUS Study Group.

Characteristic	Melanoma Patients (n = 58) (%)
Age at Delivery [Years]	
Mean ± SD	32.93 ± 6.04
Range	18–43
Primary Site	
Lower Extremity	16 (31.37)
Trunk	15 (29.41)
Upper Extremity	10 (19.61)
Head and Neck Area	9 (17.65)
Uvea	1 (1.96)
Not Reported	7
Breslow [mm]	
Mean ± SD	3.39 ± 2.74
Range	0.7–12
Mutation	
BRAF	30 (68.18)
NRAS	4 (9.09)
Wildtype	10 (22.73)
Not Reported	14
Melanoma Type	
Nodular	19 (52.78)
Superficial Spreading	11 (30.56)
Spitzoid	4 (11.11)
Acral lentiginous	1 (2.78)
Uveal	1 (2.78)
Not Reported	22
Stage at Primary Diagnosis	
I	10 (17.86)
II	12 (21.43)
III	23 (41.07)
IV	11 (19.64)
Not Reported	2
Death after Delivery [Days]	n = 24 (41.38)
Mean ± SD	515.5 ± 430.9
Range	18–1746

In 45 women (78.95%), metastases were discovered, and in 15 of those cases metastases involved major parts of the abdomen and pelvis and were thus in close proximity to the uterus. Therapy during pregnancy only took place in 3 cases, one consisting of surgery, one of vemurafenib, and one of tumor antigen loaded dendritic cells. Of the melanoma patients, 24 (41.38%) died from their disease.

Infant characteristics are summarized in Fig. 1. All 67 live-born children were included, and twins were considered individually. There were 26 females (46.43%) and 30 males (53.57%) among the children for whom sex data was available. No infant showed clinical evidence of maternal melanoma metastasis at time of birth. Careful screening of the placenta was reported in only 23 cases (44.23%). Except for one case of villitis and one case of hypertrophic hyperemia, all placentas presented inconspicuous with no evidence of melanoma and no villous invasion. The mean follow-up time of the children was 30.28 months (range, 0 days to 12 years). One child born at 25 gestational weeks died 2 days postpartum, probably due to prematurity. It was not stated if the child was autopsied. All other children remained alive and without evidence of melanoma until the last date of contact.

3.2. Comparison group: historical case reports

An overview of all cases of placental and fetal metastasis of maternal melanoma described in the literature is given in Table 2. Gross and microscopic metastasis to the placenta was reported in 10 cases, microscopic metastasis in 27 cases. During the period from 1930 to 2019, there were 14 patients reported with vertical transmission of melanoma metastases to the fetus.

Maternal characteristics are summarized in Table 3. Mother's ages at delivery ranged from 25 to 39 years (M = 30.27, SD = 4.13). For all affected women, the disease progression resulted in death. On average, the mother died approximately 11 weeks after delivery (range, 2 days to 10 months).

The characteristics of all 14 children with maternal melanoma metastases are summarized in Table 4. Eight of the 13 (61.54%) affected children for whom sex data was available were male. Mean gestational age at birth was 33.5 weeks (range, 27–40 weeks) and 81.82% of the infants were born by cesarean section, the main reason being maternal deterioration. In 3 cases, both gross and microscopic invasion of the placenta were described; these same cases also reported villous invasion. Microscopic examination revealed maternal melanoma metastases in 3 placentas, five placentas were explicitly not examined. Regarding the primary site of presentation, 8 of the 14 maternally derived melanoma metastases presented in the head and neck region, 4 of those involving the temporal bone. Metastatic spread was reported in 10 of the 14 cases and occurred particularly frequently in the lungs, liver, and brain. The age of metastatic presentation at the child ranged from time of birth to 9 months and was 4.33 months on average. In 10 cases (71.43%), transplacentally transmitted melanoma was fatal to the offspring at some point. Attempted therapies consisted of surgery, skin grafts from mother and grandmother, and chemotherapy (temozolomide in one case, vemurafenib in one case), all without long-term success. Excluding 2 stillbirths, mean survival after diagnosis was 40.3 weeks and ranged from 2 weeks to 28 months. One case presented a remarkable situation in particular: in a dichorionic diamniotic twin pregnancy, one of the twins (both female) was affected by maternal melanoma metastases and died in utero; the other infant was born without evidence of disease [7]. Regression occurred in 4 cases (28.57%, 2 female and 2 male infants), in 3 of these after treatment and in one spontaneously. Treatment consisted of ifosfamide and adriamycin in 2 children and surgery in one child. In 3 of the surviving children, the vertically transmitted melanoma initially presented on the temporal bone. Long-term follow-up was performed in all 4 cases for an average of 8 years (range, 2–14 years). Those children showed no evidence of disease up to this point.

3.3. Statistical analysis

Mothers in the historical comparison group were on average almost 3 years younger by the time of delivery (30.27 years versus 32.93 years), however, this difference is not statistically significant ($p = 0.1731$). Melanoma mutation and localization, when reported, occurred in comparable proportions in both groups. As to be expected, the mothers of the historical comparison group died more frequently from their disease ($p < 0.0001$). Also, time of death after delivery was on average 62.47 weeks earlier than in women belonging to the new data and thus differed significantly ($p = 0.0004$). When comparing the infant characteristics, no relevant difference could be found in either gestational age at birth, birth type, or sex. When calculating the odds ratio to determine the association between sex and outcome of the child, a twice as high risk of dying from maternal melanoma metastases was found for male infants. However, due to the small group size, this risk is not statistically proven. As 10 children in the historical comparison group died from maternal melanoma metastases and all but one child in the new datasets survived, the child outcome was significantly different ($p < 0.0001$). In the affected children, there was a clustering of the vertically transmitted melanoma localization at the head and neck and especially the temporal bone, which, however, cannot be statistically validated due to the small group size.

4. Discussion

4.1. Risk evaluation

The risk of transmission of maternal melanoma metastases to the unborn child seems to be much lower than anticipated based on former studies. Even children born to women with considerable abdominal tumor burden did not show any evidence of transplacental transmission. It also appears that the risk of placental involvement is very small.

Table 2
Summary of patient cases reporting placental or fetal metastasis of maternal melanoma [7–55].

Year	Reference	Placental Findings	Infant Outcome
1918	Markus[8]	G/M	Death 12 hours, presumed prematurity
1930; 1949	Weber[9]; Holland[10]	G/M	Death 10.25 months, melanoma
1940	Gottron[11]	N/ME	Death 5 months, melanoma
1950	Dargeon[12]	N/ME	Death 10.5 months, melanoma
1954	Byrd[13]	M	Death 24 hours, presumed prematurity
1955	Reynolds[14]	M	NED 10 months
1960; 1961	Freedman[15]; Moschella[16]	G/M	NED 2 years
1963	Aronsson[17]; Cavell[18]	N/ME	NED 2 years, melanoma with spontaneous regression
1965	Brodsky[19]	G/M	Death 48 days, melanoma
1971	Stephenson[20]	M	NED 2 years
1975	Holcomb[21]	M	NED 47 days
1976	Sokol[22]	G/M	Death 2 days, prematurity
1976	Smythe[23]	M	NED 9 months
1976	Gilis[24]	G/M	NED 2 years
1977	Russell[25]	G/M	NED 5 months
1979	Looi[26]	M	NED 1 month
1986	Moller[27]	G/M	NED 6 months
1987; 1989	Machin; Anderson[28]	M	NED 1 year
1994	Brossard[29]	M	NED 1 year
1996	Marsh[30]	M	NED
1996	Dillman[31]	M	NED
1997	Baergen[32]	M	NED 7 months
1997	Dipaola[33]	M	NED 17 months
1998	Johnston[34]	M	NED 1 year
1998	Ferreira[35]	G/M	Stillborn, presumed melanoma
1998	Merkus[36]	M	NED 4 years
2002	Alexander[37]	M	NED 10 months
2003	Altman[38]	M	NED 19 months
2005	Trumble[39]	N/ME	Death 25 months, melanoma
2007	Lakshminarayana[40]	M	NED 10 months
2008	Shuhaila[41]	G/M	NED 18 months
2008	Yeung[42]	M	Death several weeks, necrotizing enterocolitis
2009	Pérez[43]	M	NED 20 months
2010	Perret-Court[44]	M	NED 5 months
2010	Pagès[45]	M	NED 50 months
2010	Raso[46]	No metastasis	Melanoma, regression, NED 12 years
2010	Valenzano Menada[47]	M	Melanoma, regression, NED 24 months
2012	Naidu[48]	M	Death 2 years, melanoma
2012	Sekulic[49]	N/R	Death 33 months, melanoma
2014	De Carolis[50]	M	Death 4.5 months, melanoma
2017	Mendizabal[51]	M	Death 2 weeks, hyaline membrane disease, pulmonary hemorrhage, and necrotizing enterocolitis
2017	Poreau[52]	M	NED
2017; 2019	Pourtsidis[53]; Chrysouli[54]	N/ME	Melanoma, regression, NED 4 years
2018	Menzer[55]	M	NED 1 year
2019	Canu[7]	N/R	Stillborn, melanoma

Abbreviations: G, gross metastasis present; M, microscopic metastasis present; N/ME, no microscopic examination; NED, no evidence of disease; N/R not reported; grey, fetal metastasis

Authors in case reports from 1930 to 1998 assumed a maternal origin of the metastasis primarily based on the clinical and histologic similarity of the tumors in mother and child. The diagnosis of vertical transmission in those older cases was supported by the fact that melanomas in neonates are an absolute rarity, and no primary tumor could be found in the infants. In articles from 2005 onward, the evidence for vertical transmission of melanoma was more conclusively provided by PCR [46,47,49,53,54] and fluorescent in situ hybridization in conjunction with karyotyping, especially in male fetuses whose tumor cells revealed karyotype XX [39,46,47].

The question arose whether the tumor burden of the placenta was related to an increased likelihood of fetal transmission. Since the child was affected in only 6 out of 37 cases with verified placental melanoma metastases (16.22%), and only 3 of the 14 cases with fetal metastases

Table 3
Summary of reported cases with mother-to-infant transmission of melanoma: maternal characteristics.

Ref.	Year	Age at Delivery	Breslow	Mutation	Primary Site	Placental Findings	Villous Invasion	Survival after Delivery
Weber [9]; *Holland* [10]	1930; 1949	27	N/R	N/R	Left thigh	Gross & microscopic	Yes	55 days
Gottron, Gertler [11]	1940	25	N/R	N/R	Right back	N/ME	N/R	2 months
Dargeon et al. [12]	1950	28	N/R	N/R	Right leg	N/ME	N/R	4 days
Cavell; Aronsson [18]	1963	27	N/R	N/R	Diffuse at autopsy	N/ME	N/R	4 days
Brodsky et al. [19]	1965	28	N/R	N/R	Mid-interscapular region	Gross & microscopic	Yes	17 days
Ferreira et al. [35]	1998	33	10.7 mm	N/R	Left shoulder	Gross & microscopic	Yes	2 days
Trumble et al. [39]	2005	N/R	N/R	N/R	N/R	N/ME	N/R	N/R
Raso et al. [46]	2010	N/R	N/R	N/R	N/R	None	N/R	Several weeks
Valenzano et al. [47]	2010	28	N/R	N/R	Right gluteus	Microscopic	N/R	2 weeks
Naidu et al. [48]	2012	N/R	N/R	BRAF V600E	Face	Microscopic	N/R	8 months
Sekulic [49]	2012	33	N/R	BRAF V600E	N/R	N/R	N/R	10 months
De Carolis et al. [50]	2014	31	N/R	N/R	Left back	Microscopic	N/R	12 weeks
Pourtsidis [53]; *Chrysouli* [54]	2017; 2019	34	N/R	BRAF V600E	N/R	N/ME	N/R	3 months
Canu et al. [7]	2019	39	0.75 mm	NRAS Q61X	Left arm	N/R	N/R	N/R

Abbreviations: N/R, not reported; N/ME, no microscopic examination.

Table 4
Summary of reported cases with mother-to-infant transmission of melanoma: fetal characteristics.

Ref.	Gestational Age at Birth (weeks)	Sex	Birth Type	Outcome	Primary Site of Presentation	Age at Presentation (months)	Therapy	Survival after Diagnosis	Follow-Up
Weber [9]; *Holland* [10]	38	m	CS	Death	Subcutaneous nodules	8	N/R	2,25 months	N/A
Gottron, Gertler [11]	term	m	N/R	Death	N/R	5	N/R	14 days	N/A
Dargeon et al. [12]	8 months	m	CS	Death	Ear canal	9	Surgery	1,5 months	N/A
Cavell; Aronsson [18]	34	f	PML	Regression	Soft tissue tumors in legs	2	N/R	Alive	14 years, NED
Brodsky et al. [19]	38	m	CS	Death	Skin lesions on chest wall	birth	Skin grafts	37 days	N/A
Ferreira et al. [35]	28	N/R	CS	Death (stillborn)	Multiple skin lesions	birth	N/A	N/A	N/A
Trumble et al. [39]	N/R	m	NSVD	Death	Posterior cranial fossa	7	Surgery, Temozolomide	18 months	N/A
Raso et al. [46]	N/R	m	N/R	Regression	Middle ear, temporal bone	6	Ifosfamide, Adriamycin	Alive	12 years, NED
Valenzano et al. [47]	31	m	CS	Regression	Mastoid	3	Ifosfamide, Adriamycin	Alive	2 years, NED
Naidu et al. [48]	term	f	CS	Death	Skin lesions on scalp and buttocks	1.5	Radiation, BRAF inhibitor	2 years	N/A
Sekulic [49]	N/R	f	N/R	Death	Skin lesion on forehead	5	Surgery, Verumafenib, Radiation	28 months	N/A
De Carolis et al. [50]	27	m	CS	Death	Brain	4	N/R	15 days	N/A
Pourtsidis [53]; *Chrysouli* [54]	33	f	CS	Regression	Mastoid cavity	8	Surgery	Alive	4 years, NED
Canu et al. [7]	32	f	CS	Death (stillborn)	Subcutaneous nodules	birth	N/A	N/A	N/A

Abbreviations: term, 37 or more weeks of pregnancy; N/R, not reported; N/A, not applicable; m, male; f, female; CS, cesarean section; PML, premature labor; NSVD, normal spontaneous vaginal delivery; NED, no evidence of disease.

(21.43%) also showed gross involvement of the placenta, we were not able to confirm this hypothesis. Maternal death within a few months after birth seems to be an indicator for an unfavorable fetal or infant outcome, which can probably be attributed to the higher tumor burden and the associated increased likelihood of metastasis. Regarding child characteristics, no correlation between gestational age at birth and the occurrence of melanoma metastases in the fetus was identified. An association between male sex of the infant and an increased risk of developing metastases of any maternal cancer has been described repeatedly in the literature [6,28], but could not be statistically confirmed by our analysis. It is remarkable that the head and neck area and especially the temporal bone (including mastoid and ear canal) of the infants were particularly frequently affected by melanoma metastases. The temporal bone and the mastoid cavity are very uncommon sites for cancer metastases, and it remains unclear why they seem to be predestined for the establishment of maternal melanoma metastases.

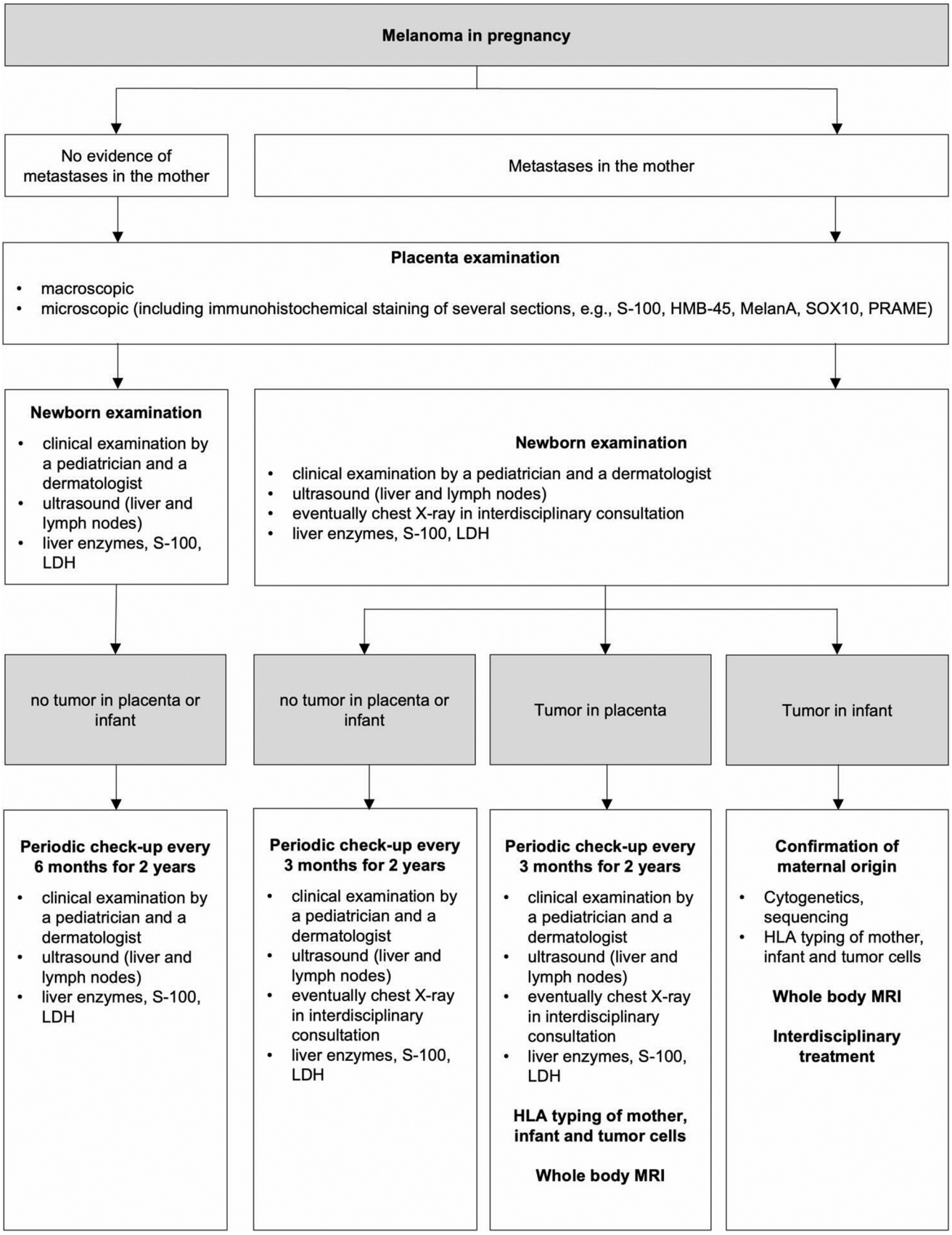

Fig. 2. Diagnostics and surveillance recommendations for children born to women with metastatic melanoma.

However, it should also be noted that in 3 of the 4 children who experienced regression, the melanoma metastases were located on the temporal bone, which makes this a possible indicator for a favorable child outcome.

4.2. Limitations

It remains to be mentioned that some factors may have contributed to a possible bias in the risk assessment of vertical transmission of malignant melanoma. Some case reports date back a very long time, and the comparison group is very small. Some data were missing, and a systematic follow-up of the children did not take place in all our cases. Decreasing autopsy rates, also with regard to neonates [56], can lead to maternal melanoma metastases in deceased infants not being detected.

4.3. Vertical cancer transmission

Apart from malignant melanoma, mother-to-child transmission of cancer cells has also been reported for leukemia and lymphoma, lung cancer and cervical carcinoma. The emerging question of how transplacental spread of maternal metastases can occur in the first place is poorly understood. The rare nature of the occurrence suggests that several factors must be present simultaneously. Not only must the maternal tumor be able to invade fetal tissue, but also the immune system of the infant must fail to reject the tumor cells adequately. Considering the frequency of different tumor types in fetal metastasis, melanoma seems to have a particularly distinct ability to spread to the placenta and fetus relatively to other malignancies.

4.4. Surveillance and treatment recommendations

Diagnostics and surveillance recommendations for children born to melanoma patients are shown in Fig. 2. For neonates that show no evidence of metastases at birth, we consider a periodic check-up including clinical examination, ultrasound, and laboratory tests for 24 months postpartum to be adequate, since melanoma metastases in the infant presented after 9 months at the latest in the historical case reports. A chest X-ray should be performed under interdisciplinary consultation and only in children at high risk for vertically transmitted metastases. If the lung results are questionable, a low-dose CT/MRI may follow. For children up to 6 months a “feed and swaddle” method, where the infant is fed and allowed to fall asleep before the low-dose CT/MRI, anesthesia with its associated risks can be avoided [57]. Regarding the therapy of metastatic melanoma, young children are usually excluded from clinical trials and recommendations are therefore based mainly on limited case reports and extrapolation from studies of management in adult patients [58]. Adjuvant therapy for children under 12 years at risk for maternal melanoma metastases lacks sufficient data and therefore cannot be recommended.

4.5. Conclusion

In conclusion, the risk for transplacental transmission of maternal melanoma cells is extremely low. Our data are well suited to relieve pregnant melanoma patients of some fear, at least for their infant. Nevertheless, this article is intended to arise awareness among physicians about vertical transmission of cancer, and to encourage a careful examination of the placenta and the child.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcskn.2023.100005.

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