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Melanoma and Pregnancy

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1. Introduction

Melanoma is one of the most commonly diagnosed cancer during the childbearing age and during pregnancy. It is also the malignancy that is most often reported in the literature in association with placental and/or foetal metastasis (Alexander et al., 2003).
The coexistence of melanoma and pregnancy is therefore not an exceptional situation, difficult to manage, raising numerous questions in terms of prognosis, feasibility of the different imaging and radio-diagnostic investigations, and of the various modes of treatment. On the other hand, when melanoma is diagnosed during the childbearing age, out of the immediate context of pregnancy, several questions are raised regarding the potential consequences on the evolution of melanoma of being pregnant later on.

2. Epidemiological data

Cancer is now among the leading causes of non-accidental death in women of child-bearing age. In the USA, malignancy accounts for about 19% of mortality in women aged between 15 and 34 years (Pavlidis, 2002). The most frequently observed cancers among young women of child-bearing age are breast cancer, cervical cancer, malignant haemopathies (Hodgkin's disease and leukaemia) and melanoma (Langagergaard, 2011).
In France, between 1980 and 2000, the standardized worldwide population incidence rate of melanoma increased from 3,9 to 9,5/100,000 persons/year among women. In 2000, the estimated number of new cases of skin melanoma was 7,231, with 58% diagnosed in women. The incidence increased by a factor of 3,2 among men and by a factor of 2,4 among women. Despite this greater increase among men, incidence remained higher among women across the whole period (Grange, 2005). In Denmark, for instance, the incidence of melanoma among women between the ages of 15 and 34 increased by 4,3% per year on average from 1970 to 1999 (Van der Horst et al., 2006). Altogether, it is estimated that about one third of all melanomas in women is diagnosed during their childbearing years (Langagergaard, 2001).
In Western countries, women often postpone childbearing for different reasons (Langagergaard, 2011) and because the incidence rates of most cancers increases with advancing age, more women can therefore be expected to be diagnosed with cancer before childbearing or during pregnancy. Although the exact incidence and prevalence are unknown, estimates suggest one to two new cases of cancer in every 1,000 pregnancies (Alexander, 2003). The most frequently encountered cancers during pregnancy are in line with those the most frequently described among young women of childbearing age: for breast and cervical cancer, the incidences estimated per number of pregnancies are of the

order of 1/2,000 to 1/10,000; for lymphomas, the incidence is estimated at 1/1,000 to 1/6,000. The incidence of melanomas in pregnancy is estimated at 1/1,000 to 1/10,000, and melanoma is thought to amount to around 8% of cancers diagnosed during pregnancy (Oduncu et al., 2003).

However, the real incidence of cutaneous melanoma occurring in pregnancy is still not known. Lens et al., 2004 examining the data from the Swedish National and Regional Cancer and Mortality Registries found that, among 19,337 women diagnosed with cutaneous melanoma in the period from 1958 to 1999, 28,6% were diagnosed with melanoma during their reproductive period, while only 0,9% of the women were diagnosed with melanoma during pregnancy. Stensheim et al., 2009 used the Cancer and Medical Birth Registry of Norway to assess 42,511 women (516 pregnant) aged to 16 to 49 with various cancers. The most commonly diagnosed cancer during pregnancy was melanoma.

3. Melanoma and influence of hormonal factors

For many years, there have been concerns that hormonal and immunological changes occurring during pregnancy may be important in the development of melanoma. Changes in pigmentation are associated with pregnancy, oral contraceptives and hormone replacement therapy. These observations have led to speculation concerning a relationship between hormones and melanoma.

3.1 Exogenous female hormones

Numerous epidemiological studies have questioned whether the use of oral contraceptives (OCs) or hormone replacement therapy (HRT) could increase a woman's risk for melanoma. Risk is expressed as an estimate of relative risk (RR) or odds ratio (OR). OR is the odds of melanoma occurring in women exposed to OCs/ odds of melanoma occurring in those not exposed to OCs. These studies showed conflicting results: a recent case-control study of OCs and risk of melanoma (Koomen et al., 2009) suggests a cumulative dose-dependent increased risk of melanoma with the use of OCs: 778 cases and 4,072 controls were included; melanoma risk was significantly associated with estrogen use (≥ 0.5 year; adjusted OR= 1,42, 95% CI 1,19-1,69). The major limitation of this study was the lack of information concerning sun exposure, skin type, sunburn history which are important potential confounders. However, in their review of the literature, Gupta et al. (Gupta δ Driscoll, 2010) identify 22 studies that have explored whether or not OCs enhance a woman's risk for melanoma, and most have not shown an effect of use of OCs at some time in life compared with women who never used OCs. No studies have specifically reported the impact of OCs on prognosis for women diagnosed with melanoma. The data concerning HRT and melanoma risk are more limited than for OCs, but most of these studies have shown no effect of HRT (Gupta δ Driscoll, 2010).

In summary, current clinical evidence does not suggest that exogenous female hormones contribute significantly to increased risk of melanoma.

3.2 Endogenous female hormones

The effects of high concentrations of oestrogen as a result of pregnancy on melanogenesis have long been debated, leading to different questions: is there an influence on melanoma prognosis if a woman is diagnosed with it during pregnancy? Should women with a

previous history of melanoma avoid subsequent pregnancies in order to limit the risks of local or systemic recurrences?

3.2.1 Prognosis of melanoma diagnosed during pregnancy

Many studies since the 1980s have investigated whether survival was impacted in women diagnosed during pregnancy with melanoma classified as localized stage I or II according to the American Joint Committee on Cancer, AJCC (Balch et al., 2001). Randomized or non randomized clinical trials to assess the implication of pregnancy in women with cutaneous melanoma do not exist. In the literature, there is population-based studies or consecutive or non-consecutive case series ; these studies assess survival rates between pregnant women with melanoma compared to age adjusted non pregnant women. Two recent population - based studies addressed the question of whether pregnancy adversely affects survival in melanoma patients. Lens et al., 2004 reported on 185 patients from the Swedish Cancer registry who were pregnant at the time of diagnosis of localized melanoma. The outcome of these patients was compared with 5,348 non-pregnant age- and gender-matched controls. Multivariate regression analysis showed that pregnancy at the time of melanoma diagnosis was not a significant variable in relation to overall survival. Authors noted that pregnant melanoma patients had somewhat thicker melanomas, with a mean Breslow thickness of 1,28 mm versus 1,07 mm in controls.

A second population-based study (O'Meara et al., 2005) used the database from the California Cancer Center to evaluate "pregnancy-associated melanoma", specified as a woman diagnosed with melanoma during pregnancy or within 1 year after delivery (post partum group). The control group was an age-matched group of patients who were not pregnant at the time of diagnosis. The median Breslow thickness was 0,77 mm in pregnant patients, 0,9 mm in post partum patients and 0,81 mm in the controls. O'Meara et al., 2005 found no evidence of a decrease in survival of patients who were pregnant (HR=0,79;P=0.570) or post partum compared to controls. The size of the study population is a strength, but one limitation is that approximately 20% of the Breslow thickness data were missing for both the study and the control group and we cannot extrapolate therefore whether the groups were well balanced or not regarding this important prognosis marker.

In the most recent population-based study, Stensheim et al., 2009 used the Cancer and Medical Birth Registry of Norway to assess 42,511 women (516 pregnant) aged to 16 to 49 with various cancers. The cancer most commonly diagnosed during pregnancy was melanoma. When compared to age- and gender-matched non pregnant controls, there was a slightly increased cause-specific death rate if melanoma was diagnosed during pregnancy. No difference in Breslow index was found between the two groups; however the Breslow thickness was collected for only 55% of the pregnant patients.

The details of the other studies and the results are presented in Table 1. Altogether, no statistically significant difference in survival rates between women diagnosed with melanoma during pregnancy and women diagnosed with melanoma out of pregnancy was established, suggesting that pregnancy does not favour the development of more aggressive melanoma.

There are little data to address the question of whether pregnancy has a negative effect on survival in patients with more advanced disease. In a study reported by Shiu et al., 1976, 14 patients with regional stage III AJCC melanoma diagnosed during pregnancy were found to have an important decrease in survival compared with 11 regional stage III AJCC melanoma

nulliparous patients. The 5-year survival was 29% for the pregnant patients and 55% for the control group, not statistically different, but very small numbers of patients were involved. We recently observed that the 2-year survival rate in 16 AJCC stage III patients diagnosed during pregnancy was 56% (Pagès et al., 2010), which is close to that reported in the literature for those not pregnant (Balch et al., 2001); the AJCC stage IV (6 patients) 2-year survival rate was 17% which was shorter than that reported in the literature (Balch et al., 2001). Nevertheless, this data does not make it possible to draw definitive conclusions, on account of the small sample number and the absence of a control group in our study.

Authors	Number of patients diagnosed with melanoma during pregnancy (Group 1)	Number of patients diagnosed with melanoma out of pregnancy (Group 2)	Breslow thickness (mm) Group 1 / Group 2	Survival rates between groups	Follow-up time
Reintgen et al. 1985	58	585	1,90/ 1,51	NS	5 y (mean)
McManammy et al. 1989	23	243	1,62/ 1,72	NS	2 mo-20 y
Wong et al. 1989	66	619	1,24/ 1,28	NS	NR
Slingluff et al. 1990	100	86	2,17/ 1,52	NS	6 y (mean)
MacKie et al. 1991	92	143	2,38/ 1,96	NA	NA
Daryanani et al. 2003	46	368	2/ 1,70	NS	106 mo (median)
Lens et al. 2004	185	5348	1,28/ 1,07	NS	11,6 y (median)
O'Meara et al. 2005	149	Within 1 year postpartum: 263 Non pregnant: 2,451	0,77/0,90/ 0,81	NS	2-10 y

Abbreviations: Mo: months; y: years; NA: not available, NS: statistically non-significant difference in survival rates between groups.

Table 1. Controlled studies evaluating the impact of pregnancy on survival in women with AJCC stage I/II melanoma.

3.2.2 Impact of subsequent pregnancy on melanoma prognosis

A small number of studies have addressed the impact of pregnancy after a diagnosis of melanoma. One of them (Lens et al., 2004) was a secondary analysis within a large retrospective cohort study of Swedish patients: 966 women who became pregnant after melanoma diagnosis were compared with 4,567 women without pregnancies subsequent to the melanoma diagnosis. A multivariable Cox regression model showed that pregnancy after melanoma diagnosis was not related to survival (Hazard Ratio for death in women who had pregnancy subsequent to the diagnosis of melanoma: 0.58, 95% CI= 0.32-1.05). Based on the current evidence, there is no reason to recommend deferral of subsequent pregnancy in women diagnosed with localized melanoma. Counselling women on subsequent pregnancies should be based upon well-known prognostic factors, such as Breslow thickness and ulceration (Balch et al., 2001). In women with thick tumours (over 1.5 mm), it may be recommended to discuss with the patient the fact that if melanoma recurs it is more likely to do so in the first 2 years; physicians can thus advise these women to delay pregnancy for 2 to 3 years.

Altogether, the issue of whether hormones influence malignant melanoma has been controversial for many years. There is no evidence that pregnancy adversely affects outcome in melanoma patients who have clinically localized disease. Continuing to recommend a postponement of childbearing for these patients is not supported by available clinical evidence suggesting an increased risk of cancer progression due to pregnancy itself. For more advanced disease, recommendations must be based on individual patients and their wishes.

4. Maternal-foetal transmission of melanoma during pregnancy

Only disseminating, metastatic cancers appear to be liable to produce placental and foetal metastasis, in an haematogenic way. The real incidence rates for placental and foetal metastasis, and the natural history of cancers during pregnancy, are still little known. In France, for instance, there are no epidemiological surveillance tools for cancers among pregnant women. In the literature, irrespective of type of cancer, about a hundred cases of placental metastasis (excluding cases of foetal origin and trophoblastic disease) have been described since 1866 (Dessolle et al., 2007). Alexander et al. in a literature review reported 87 cases of placental metastasis secondary to maternal cancer. In this study, melanoma was the cancer the most frequently responsible for this type of development: 27 cases out of 87 (31%). Given the possibility of placental metastasis, the placenta should be very carefully examined, both macroscopically and microscopically in case of metastatic melanoma in the mother.

Furthermore, the placenta represents an ideal site for metastases during gestation, because of its vascularisation, its large surface area and its biological environment and also because of its hyperkinetic state associated with pregnancy.

Table 2 sums up the cases of placental and/or foetal metastasis in connection with melanoma described in the literature and is an actualisation of the table presented in the paper of Alexander et al. Of the 27 placentas subjected to anatomo-pathological investigation, 17 cases of microscopic placental metastasis are reported, without any anomaly being macroscopically visible. The microscopic examination of the placenta should be as thorough as possible: in the case reported by Baergen et al, the placental metastatic localisations were visible on only 3 of the 50 sections performed, in the case reported by

Valenzano Menada et al. the microscopic examination with normal staining of the placenta showed no particular anomaly and the micro-metastases were only visualised by the mean of immuno-histo-chemical analyses (PS100).

Considering now the problematic of foetal metastasis secondary to maternal cancer, according to the review of the literature by Dessolle et al, 15 cases have been published since 1866. Several types of cancer have been incriminated: among the 15 cases, 5 foetal metastasis were secondary to maternal melanoma, 5 to acute leukaemia or lymphoma, 2 to bronchial cancer, 2 to sarcomas and one to a non-specified maternal cancer. Thus, although foetal metastasis in case of disseminated cancer in the mother is an exceptional situation, melanoma does appear as the most frequent cause. The study by Alexander et al. collates 6 reports of foetal metastasis secondary to maternal metastatic melanoma. Two further cases of foetal metastasis (Trumble et al., 2005 and Valenzano Menada et al., 2010) have been further reported. Among these 8 cases (Weber et al., 1930 Holland et al., 1949 Gottron et al., 1940 Dargeon et al., 1950 Aronsson Cavel et al., 1963 Brodsky et al., 1965 Ferreira et al., 1998 Trumble et al., 2005 Valenzano Menada et al., 2010), tumoral encroachment on the placenta was observed for 4. The 4 remaining cases were not examined in this respect. These 8 observations, although some are incomplete, enable the following characteristics:

- Melanoma metastasis appearance occurring shortly after birth, with a mean time lapse of around 3 months (age at diagnosis ranging from 1 day to 9 months, missing data for 1 case).
- Relatively homogeneous clinical presentation of metastatic proliferation to the child: the neonatal metastases were for the most part in the form of subcutaneous metastatic nodules, or intra-abdominal tumoral masses; there are exceptions for the cases published by Trumble et al. and Valenzano et al, where intracranial proliferations were diagnosed at 7 and 3 months after birth, respectively.
- Extremely poor prognosis, as the large majority of the infants died before the age of 1 year, with the exception of two cases (Aronsson, Cavell et al., 1963 and Valenzano Menada et al., 2010) of secondary regression of the metastatic disease in the children. In the case published by Aronsson and Cavell, spontaneous resolution of pulmonary and subcutaneous metastases occurred at 13 weeks after birth; the remission was secondarily confirmed during follow-up, with the child presenting no particular heath problem at the age of 14 years. Valenzano Menada et al. reported the case of a regression of intracranial and pulmonary metastases at 5 months after birth following initial failure of chemotherapy associating ifosfamide and adriamycine (1 month after discontinuation of chemotherapy). Complete remission of the disease was later confirmed when the child was seen at 24 months, with no residual signs of disease.
- Predominance of male children: 6 cases out of 8, one girl and one stillborn child whose gender was not reported.

5. Management of melanoma in a pregnant woman

Diagnosing melanoma during pregnancy will raise several questions, depending notably of the stage of malignancy (primary melanoma, lymph node metastasis, visceral metastasis, type of visceral metastasis) and of the gestational age. One of the first step will be the evaluation of the extent of the cancer and will raise the question of the feasibility of some radiological diagnosis procedures and another step will be the feasibility of the oncologic treatment (surgery, adjuvant therapy with immunotherapy, radiotherapy, chemotherapy…).

Authors	Placental Findings: Macroscopic involvement/ Microscopic involvement	Post delivery maternal survival	Existence of fetal metastases/ age at diagnosis	Infant outcomes/ follow -up
Weber et al., 1930, Holland et al. 1949	+/+	2 m	+/ 8 m	Death 10.5mo
Gottron et al., 1940	NE	2 m	+/ NR	Death 5 mo
Dargeon et al., 1950	NE	4 d	+/ 9 m	Death 10 mo
Aronsson et al. , Cavell et al., 1963	NE	4 d	+/ 2 m	Melanoma Regression, Alive (14 years follow up)
Brodsky et al., 1965	+/+	17 d	+/ 11 j	Death 48 d
Ferreira et al., 1998	+/+	2 d	+/ 1 j	Stillbirth
Trumble et al., 2005	NE	NR	+/ 7 m	Death 25 mo
Valenzano Menada et al., 2010	-/+	15 d	+/ 3 m	Melanoma Regression Alive (24 mo follow up)
Markus et al., 1918	+/+	5 h	No	Death 1 d*
Byrd et al., 1954	-/+	21 d	No	Death j*
Reynolds et al., 1955	-/+	1 m	No	Alive/ 10mo
Freedman et al., 1960	+/+	1.5 m	No	Alive/ 24mo
Stephenson et al., 1971	-/+	3m	No	Alive/ 24mo
Holcomb et al., 1975	-/+	18 d	No	Alive/ 3mo
Sokol et al., 1976	+/+	54 d	No	Death 2 d*
Smythe et al., 1976	-/+	20 d	No	Alive/ 9mo
Gillis et al., 1976	+/+	7.5 m	No	Alive/ 24mo
Russel et al., 1977	+/+	15 d	No	Alive/ 5mo
Looi et al., 1979	-/+	48 d	No	Alive/ 1mo
Moller et al., 1986	+/+	30 d	No	Alive/ 6mo
Anderson δ Machin 1989	-/+	6 m	No	Alive/ 12mo

Authors	Placental Findings: Macroscopic involvement/ Microscopic involvement	Post delivery maternal survival	Existence of fetal metastases/ age at diagnosis	Infant outcomes/ follow -up
Brossard et al. 1994	-/+	4 d	No	Alive/ 12mo
Marsh et al., 1996	-/+	21 d	No	Lost to follow up
Dillman et al.,	-/+	5 m	No	Lost to follow up
Baergen et al. 1997	-/+	7 d	No	Alive/ 7mo
Dipaola et al., 1997	-/+	1 m	No	Alive/ 17mo
Jonhston et al., 1998	-/+	4 d	No	Alive/ 12mo
Merkus et al., 1998	-/+	2 m	No	Alive/ 48mo
Altman et al., 2003	-/+	19 m	No	Alive/ 19mo
Alexander et al., 2004	-/+	56 d	No	Alive/ 10mo
Pagès et al., 2010	+/+	3,5 m	No	Alive/ 56mo

Abbreviations : NE: not examined, NR : not reported, d: days, mo: months ,
* : cause of death = prematurity.

Table 2. Placental and/or foetal melanoma metastases.

The question of the maternal prognosis will be central and the opportunity of pursuing or not the pregnancy will be asked by the patient, her family and the medical staff.

5.1 Radiological diagnosis in pregnant women

A recent review (Lazarus E. et al., 2007) pointed out a 121% increase over 10 years in the use of imagery investigations requiring ionizing radiation during pregnancy, with computed tomography (CT) increasing by 25% per year. In pregnancy, the use of the irradiating techniques of classic radiology should be strictly evaluated. The French *Institut de Protection et de Sûreté Nucléaire* recalls some principles:

- In almost all cases, if a radiological diagnostic examination is considered medically necessary, the risk incurred by the mother of failure to perform such examination should be greater than the risk potentially incurred by the foetus.
- The radiation doses resulting from most diagnostic procedures usually do not present serious risk of death, malformation or altered mental development of the foetus. If the foetus is in the direct radiation beam, the procedure can often be adapted so as to reduce the foetal dose.

- When an ionizing examination is indicated in the course of which the fœtus is to be in the direct beam, and when this examination cannot be postponed until after parturition, the dose delivered to the foetus should be minimised as far as possible.
- In diagnostic radiology, the estimation of the radiation dose to the fœtus is generally not required, except when the fœtus is in the direct beam.

Thus, in most cases, irradiating radiological procedures are feasible for diagnosis or assessment of the extent of a maternal cancer (Chen et al., 2008). It is considered that the threshold fœtal irradiation dose that is potentially teratogenic is of the order of 0,1 to 0,2 Gray, Gy (Kal et al., 2005)). The radiation dose to the foetus from a typical CT study of the maternal pelvis is variable and depends on the gestational age and scanning parameters. The estimated dose of an investigation of this sort ranges from 0,024 Gy in the first trimester to 0,046 Gy in the third trimester (Pentheroudakis et al., 2006). Therefore, the radiation dose of the pelvis is likely to be below the estimated threshold level for inducing congenital malformations. Likewise, as mentioned by the International Radioprotection Commission, a foetal dose of 0,1 Gy is probably reached neither from 3 pelvic tomodensitometry examinations, nor from 20 conventional diagnostic radiographic examinations of the abdomen or pelvic area. In a review of the literature published by Pentheroudakis et al, the foetal doses received according to one or another type of ionising radiological examination performed on the mother are given, and estimated to be on average at 0,0004 mGy for chest radiography, 0,17mGy for chest tomodensitometry, and 18 to 25 mGy for abdominal-pelvic tomodensitometry. This information can be used to counsel pregnant patients who require investigation involving ionizing radiation. Nevertheless, a risk of carcinogenesis in the foetus after *in utero* irradiation always still, regardless of the dose. The baseline risk of fatal childhood cancer is 5 in 10.000 and the relative risk after exposure to 0,05 Gy is 2 (Chen et al., 2008); this relative risk may appear substantial but it should be remembered that the baseline risk is very low and that the 2004 Guidelines of the American College of Obstetricians and Gynecologists do not precisely indicate the estimated carcinogenic risk in case of irradiation *in utero,* describing it as “very small” and it is concluded that it is exceptionally unlikely that any single diagnostic radiological examination would deliver a radiation dose sufficient to justify pregnancy termination. Numerous authors agree that it can be thought that radio-diagnostic examinations in pregnant women can be performed after appropriate evaluation of the risk/benefit ratio; however, it is generally the "substitution" rule that predominates, by way of endeavours either to delay the investigation to the post-partum period, or to obtain the information required by other means, avoiding ionisation. For instance, Nicklas et al., 2000 suggest a certain number of alternatives to the standard radiographic procedures in the context of metastatic cancer in pregnant women: the use of non ionising examinations such as chest and abdominal Magnetic Resonance Imaging (MRI), to look for deep nodal involvement and evaluation of the pulmonary and liver parenchyma as an alternative to chest and abdominal tomodensitometries, and cerebral MRI for the evaluation of the central nervous system.

However, concerning MRI, the current guidelines of the U.S. Food and Drug Administration indicate that the safety of MRI with respect to the foetus « has not been established ». The risk incurred by the foetus during MRI examination without injection is on the one hand related to teratogenic effects, and on the other to the possible occurrence of damage to hearing. In view of the theoretical risk of foetal overheating/cavitation, first trimester MRI should be avoided (Chen et al., 2008) ; damaging effects could indeed arise from different

mechanisms, among which the thermal effect of magnetic resonance gradient changes and direct non-thermal interaction of the electromagnetic field with biological structures (Campbell FA et al., 2006). It should be noted that the 2007 American College of Radiology guidance document for safe MRI practices does not differentiate among the pregnancy trimesters and states that all pregnant patients can receive MRI as long as the "risk- benefit ratio to the patient warrants that the study be performed" (Kanal et al., 2007): MRI, thus, seems safe to use among pregnant women in the second and third trimesters.

The injection of contrasting substances (iodine or gadolinium) for imagery investigations is also questionable during pregnancy. Iodine-based substances belong to FDA category B. This category includes molecules for which animal studies do not show any foetal risk but for which human studies are lacking, or molecules for which animal studies have shown damaging effects on the foetus but where this effect has not been confirmed by studies among pregnant women in the first trimester of pregnancy. In animals, regarding the use of iodine-based contrast substances, no teratogenic, abortive or mutagenic effect has been reported (Webb et al., 2005). However the agents pass through the placental barrier, allowing a risk of neonatal hypothyroidism (Webb et al., 2005). This risk is only really present from the 20th week of gestation, at the time when the thyroid starts to be functional. The screening for neonatal hypothyroidism is in practice an examination that is carried out systematically by paediatric teams, but the importance of ensuring that this is indeed carried out among infants exposed *in utero* to iodine-based contrast substances should be emphasised (Chen et al., 2008).

Regarding the injection of gadolinium chelate, this is not at present authorised during pregnancy; intravenous gadolinium is teratogenic in animal studies, albeit at high and repeated doses (Chen et al., 2008). Gadolinium is classified as a category C drug by the U.S Food and Drug Administration but can be used if considered critical. In humans, knowledge on this subject relies on isolated clinical cases or small series showing no teratogenic effect (Lin et al., 2007). For instance, Marcos et al., 1997, report a series of 11 pregnant patients at terms ranging from 16 to 37 gestation weeks, who underwent MRI with gadolinium injection (gadopentatate dimeglumine: 0.1mmol/kg) for the purpose of evaluating a placental pathology, and no adverse effect was reported among the neonates. Likewise, in a prospective series of 26 pregnant patients exposed in the first trimester of pregnancy to MRI with gadolinium injection, de Santis et al., 2007, observed no abnormalities among the neonates overall. However, data is as yet insufficient in humans to justify concluding to the fact that the use of gadolinium among pregnant women is without risk for the foetus.

In practice, when there is an issue regarding whether or not investigations can be carried out for tumoral extension in pregnant women, the indications for the different examinations should be discussed one by one, taking into account the gestational stage, the anatomical area to be explored and the sensitivity of the considered radiodiagnosis tests. For instance, MRI, after injection of gadolinium chelate, is the most sensitive method for the detection of intracranial metastasis (Naggara et al., 2006)). However, as previously mentioned, the use of this contrast agent is not authorised in pregnant women. Therefore, in order to decrease the risk of false negatives, a brain scan with injection will have to be preferred to cerebral MRI without injection to look for cerebral metastases during pregnancy. Regarding the exploration of the chest, it was seen above that some authors recommend thoracic MRI. This technique is very sensitive for the exploration of the mediastinum, the heart or the rachis (Thompson et al., 2000)) but for the exploration of the pulmonary parenchyma, thoracic CT remains the first-line examination, even among pregnant women (Pentheroudakis et al.,

2006). This can be backed up if necessary, beyond the first trimester of pregnancy, by abdominal-pelvic non-injected MRI.
Therefore, although there is no general agreement regarding the initial investigations for metastatic melanoma during pregnancy, in terms of the risk / benefit balance, the association of contrast-enhanced brain and chest CT scan with abdominal ultrasonography can be proposed (Pagès et al., 2010).

5.2 Sentinel lymph node procedure and pregnancy

The sentinel node is the first lymph drainage node invaded from the primary tumour. Sentinel lymph node biopsy (SLNB) is carried out in order to determine the presence or absence of lymph-node micro-metastases in a patient without clinical adenomegalia. For melanoma, SLNB is currently considered as a staging procedure, that can be offered to the patient. In practice, the detection of sentinel node encroachment is performed by injection of a Technetium-labelled radiocolloid (isotopic method) in the area of the excision of the primary melanoma, generally the day before surgery. This injection can be coupled with a vital blue staining (colorimetric method). If the sentinel node shows micro metastasis, lymph node dissection is at present recommended.
In the literature, some publications have attempted to assess the foetal dose received during SLNB in non-pregnant women, using devices so as to mimic the different stages of pregnancy as close as possible. Thus, Gentilini et al., 2004 report a series of 26 non-pregnant patients with breast cancer and candidates for SLNB. This consisted in peri-tumoral injection of about 12 Mbq of nanocolloid ^{99m} Tc-HAS before surgery; thermoluminescent dosimeters were positioned at the injection site, between the injection site and the epigastrium, and in three other locations mimicking the position of the foetus in the different trimesters of pregnancy: epigastrium, umbilicum, and hypogastrium. The scintigraphic images showed no diffusion of the radiographic marker except at the injection point and in the sentinel node. In 23 of the 26 patients, all the measures of absorbed doses were below the dosimeter detection thresholds. For 3 patients, the doses absorbed in the epigastric, umbilical and hypogastric areas were within the following ranges: 40-320; 120-250; 30-140 µGy. The authors concluded that the foetal doses absorbed during the SLNB were negligible and that this procedure could therefore be used in pregnant women, on condition that a standardised protocol was developed. In a retrospective series of 9 patients (3 breast cancers, 6 melanomas) in whom the sentinel node procedure was performed in the course of pregnancy, Mondi et al. 2007 observed no neonatal abnormality among the newborns, while in 22% of the cases the procedure occurred in the first trimester of pregnancy. Thus the SLNB appears feasible in pregnant women, exposing the foetus to a negligible level of irradiation and hence to minimum risk. However, the concomitant use of methylene blue is still the subject of controversy in the literature, counter-indicated for some authors (Pentheroudakis et al., 2010), and envisaged for others (Pruthi et al., 2011). On the other hand, since SLNB can not currently be considered as a standard of care, except for accurate staging purpose, its realization in melanoma pregnant patient should be carefully questioned, with clear information delivered to the patient.

5.3 Treatment of melanoma during pregnancy

The optimal therapeutic strategy should be jointly discussed by the medical team, the patient and her family and will depend on gestational age, stage of cancer, treatment

options and patient wishes. It ideally requires a multidisciplinary approach with an obstetrician, a neonatologist, a medical oncologist, a surgeon and a psychologist. We will expose below the feasibility of the different therapeutical approaches usually used in melanoma during pregnancy: surgery, radiotherapy, immunotherapy and chemotherapy.

5.3.1 Surgery

Surgery in the course of pregnancy is not an exceptional occurrence. It is estimated that in the USA 1 to 2% of pregnancies will entail surgical intervention for non-obstetric purposes at some time in gestation (Kuczkowski et al., 2004). Risks to the foetus during surgery are not only anaesthesis-related, they also include intraoperative complications such as hypoxia and hypotension (Moran et al., 2007). Furthermore, decreased placental perfusion secondary to long-term positioning of the mother in the supine position is a mechanical problem in late pregnancy. Some physiological changes occurring in pregnancy have a direct impact on anaesthesic procedures, for instance :

- the total body water and plasma volume increase by about 50%, resulting in an increase in the distribution volume of hydrosoluble drugs, thus modifying their pharmaco-kinetic,
- with the increase in volume of the uterus during pregnancy, there is a decrease in the return of blood via the lower vena cava, and a risk of aortic-caval syndrome, depending on the patient's position during surgery (dorsal decubitus) which can lead to severe maternal hypotension with serious consequences on the foetus,
- gastro-intestinal motility is classically reduced during gestation with a relaxing of the lower oesophagal sphincter, presenting increased risk of inhaling gastric fluid during intubation under general anaesthetic.

The surgeon and the anaesthetist should take into account all these alterations at the time of surgery in order to avoid secondary effects on mother or foetus as far as possible. Maternal and foetal monitoring should be set up as early a possible by a trained team. Mazze δ Kallen, 1989 examined adverse outcomes after non-obstetric operations during pregnancy (data from 3 Swedish health care registries from 1973 to 1981); there were 5,405 operations in the population of 720,000 pregnant women. The incidences of congenital malformations and stillbirths were not increased in the offspring of women having an operation. However, the incidences of very- low and low- birth weight were higher in the population having surgery and attributed to the underlying cause of the emergency of surgery during pregnancy. Commonly-used anaesthetics, including nitrous oxide, enflurane and narcotics, have been extensively used safely in pregnancy (Rosen, 1999). Most authors agree that anaesthesia (general, regional or local) can be administered to pregnant women without damaging effects on the development of the embryo or fœtus. (Moran et al., 2007) With modern surgical and anaesthesia techniques, the maternal death rate is negligible and surgery during the first trimester does not appear to increase the incidence of major birth defects.

For localized melanoma, as in non pregnant patient, surgery is the mainstay of treatment for pregnant patients. With local anesthesia, local resection can occur whatever the trimester without increased risk (Richards δ Statsko, 2002). Concerning teratogenicity of local anesthesia, when administered to pregnant rats, it did not result an increased incidence of congenital malformations or adverse outcomes (Fujinaga δ Mazze, 1986). In a study of 34 pregnant women having cutaneous surgery, Gormley et al., 1990 found no maternal or neonatal adverse events in 23 mothers who were available for follow up. However, in view of the absence of adequate clinical studies in humans, it is classically recommended (when

possible and excluding emergencies) to avoid surgical interventions in the first trimester of pregnancy, or even to postpone it until after childbirth, in accordance with risk-benefit trade-off and precautionary principles, assessed for each individual case. In regard to melanoma during pregnancy, cautious but definitive treatment is recommended.

5.3.2 Adjuvant therapy with Interferon α

Patients who are at higher risk for recurrence after definitive surgery (those with thicker primary tumors and/or with primary tumor ulceration and those with lymph node involvement) should be considered for adjuvant therapy (Kirkwood et al., 1996). Interferon –α-2b (IFNα2b) is the only effective adjuvant therapy for these patients that has been approved by regulatory authorities worldwide. The safety of IFNα2b during pregnancy has not been studied formally, however low to moderate doses of interferon alpha have been safely administered in pregnant patients with chronic myeloid leukemia, CML (Regierer et al., 2006; Mesquita et al., 2005). In their review of literature, Azim et al., 2010, reported 26 CML patients exposed to IFN α during the course of pregnancy (one third during the first trimester). No congenital abnormalities were reported. Authors suggest that is probably due to IFNα high molecular weight, making it unlikely to cross the placenta. Egberts et al., 2006 reported no specific birth defects in children born to mothers receiving IFNα 2b for melanoma. It seems that IFN α can be safely administered throughout the course of pregnancy, however the potential for severe toxicity and the marginal improvement with this regimen for melanoma make its administration during pregnancy inadvisable.

5.3.3 Radiation therapy

Exposure to ionising radiation *in utero* entails a certain number of risks, and these latter vary according to the foetal dose received and the gestational age at the time of irradiation of the mother. The real dose received by the foetus depends on the size of the field irradiated, the anatomical irradiated site, the distance of the embryo or foetus from the irradiated site and the total dose prescribed. Regarding the gestational age, classically, three periods are distinguished:

- the so-called implantation period corresponding to the first 10 days after conception. During this phase, the "all or nothing" rule applies, terminating either in the loss of the embryo, or in the absence of any damage. Doses ranging from 0,05 to 0,15 Gy have been reported to increase the death rate *in utero* in studies on rats and mice (Roux et al., 1983).
- the embryogenesis or the organogenesis phase, from the 9th day to the 8th week, which involves risk of foetal malformation. These risks are related to a threshold dose of irradiation (Kal et al., 2005). Before the explosion of the atomic bomb, knowledge of radiation risks in humans relied on cases reported of pelvic irradiation in pregnant women. Thus Dekaban et al., 1968 conducted a review of the literature of published cases between 1921 and 1956 of pelvic irradiation among pregnant women, covering different terms in pregnancy (ranging from the 4th to the 25th week of amenorrhea (WA)). Twenty-six cases were analysed, with a wide variety of received doses, but, for the most part, above 2,5 Gy. Twenty children aged 3 months to 16 years were alive at the time of the last clinical examination. After exposure between the 4th and the 11th WA, numerous congenital abnormalities were reported: microcephaly, skeletal malformations, malformation of the genital organs, of the eyes (cataract,

microphthalmia, pigmentary degeneration of the retina) and damage to the central nervous system (severe mental retardation). The most frequent malformations observed among children exposed *in utero* in Hiroshima and Nagasaki was microcephaly (Stovall et al. 1995).

- the period of foetal maturation and growth, from the 8th week to the end of gestation. At this stage, the organogenesis process is complete, but the CNS and the gonads continue to differentiate and are therefore more vulnerable to irradiation. During this period, the main ionising radiation risks *in utero* are intrauterine growth delays and severe mental retardation (Otake et al., 1996).

It is however important to note that for foetal doses of 0,1 Gy, the spontaneous incidence of mental retardation, which is basically estimated to be 3%, is greater than the potential effect of radiation on the decrease in Intelligence Quotient (Streffer et al., 2003). In contrast, for foetal doses of 1 Gy, between the 8th and 15th WA, the probability of *radio-induced* decrease in IQ and mental retardation resulting from this, could be around 40%, thus superior to the spontaneous incidence (Kal et al., 2005).

In practice, after consideration of all the potentially deleterious effects for the foetus, it is at present agreed that the maximum dose should not exceed 0,1 Gy on a gravid uterus (Kal et al., 2005). Pregnancy termination in case of doses received below 0,1 Gy is therefore not justified on the basis of the irradiation risk (Pentheroudakis et al., 2010)

The other risk from irradiation *in utero*, independently of the term of pregnancy, is the one of development of solid cancers and leukaemia among children born to irradiated mothers. The spontaneous incidence of cancers and leukaemia in children aged 0 to 15 is estimated at 2-3/1,000 (Kal et al., 2005). The scale of the risk after low dose radiation and the variation of this risk according to pregnancy stage, have been the subject of numerous publications, but the interpretation of the data is still a subject of controversy. Most authors agree that prenatal exposure to ionising radiation at a dose of 0,01 Gy could increase the incidence by 40% (to reach 3-4 per 1,000) (Kal et al., 2005). It is however possible to envisage medical radiotherapy procedures in pregnant women, on condition that the foetal dose is kept to a minimum. The following recommendations should be applied:

- First, conduct an *in vitro* evaluation of the dose received by the foetus. This modelling process is based on the use of phantoms and, for data collection, on the use of thermoluminescence dosimeters.
- Secondly, depending on these latter results, set up the devices aiming to minimise the foetal dose. Useful techniques for the minimisation of foetal radiation exposure include the use of lead shielding and modification of radiotherapy techniques, including the use of multileaf collimators reducing the field size and modifying the beam energy.
- Thirdly, perform *in vivo* dosimetry.

Thus, numerous authors consider that radiotherapy can be envisaged in the course of pregnancy, in particular in certain situations such a breast cancer, supra-diaphragm Hodgkin's disease, some primary and secondary cerebral tumours, and some head and neck tumours. Indeed, as an example, the irradiation of the breast in the course of pregnancy exposes the fœtus to around 0,1 to 0,3% of the total dose (total dose estimated: 50 Gy) (Antypas et al., 1998). Luis et al. published in 2009 a review of the literature on radiotherapy administered during pregnancy, grouping their series of 9 patients with 100 cases described in the literature, irrespective of cancer type, since 1950 (sources Cochrane, Medline, PubMed). These cases excluded radiotherapy for tumour in the pelvic area, and cases of combined chemo-radiotherapy during pregnancy. Among these 109 cases, there were 13

adverse outcomes: 2 spontaneous abortions, 5 perinatal deaths, 1 stillbirth, 1 sensorineural hearing loss, 1 case of undescended testis and ventricular septal defect, 1 case of learning difficulties, 1 case of hypospadias and 1 case of delayed development. The estimated fœtal dose was reported for only 4 cases, and was below 0,1 Gy, the threshold dose thought to apply for the appearance of radio-induced fœtal malformation. The authors underline that at doses estimated to be under 0,1 Gy for *in utero* foetal exposure, the occurrence of fœtal malformations cannot be distinguished from the background rate of spontaneous congenital abnormalities. When possible, an extended follow-up of patients and their offspring should be undertaken ; in the same review of the literature, Luis SA et al. report a median duration of follow-up of 37 months (maximum follow-up : 372 months).

Although the important role of radiotherapy in achieving locoregional control and palliation in oncology is well recognised, this approach is not always incorporated into the management of melanoma. In general, patients with stage I-III melanoma (confined to the primary site and regional lymph nodes) are treated surgically with curative intent; in most cases, no further local treatment is needed. For stage IV melanoma, radiotherapy has an important role in the palliation of many symptoms (bleeding, pain, spinal cord compression from vertebral metastasis…) caused by recurrence or metastasis. Furthermore, for a few brain metastases, patients can be treated by neurosurgical resection or stereotactic irradiation. Whole brain radiotherapy after either stereotactic radiosurgery or surgical excision remains controversial (Patel et al., 2010). In most of cases, brain melanoma metastases are multiple and in this setting, high dose steroids and whole brain radiotherapy are frequently associated and provide temporary relief of symptoms (Cranmer et al., 2010). We reported 2 cases of radiotherapy during pregnancy for cerebral metastases of melanoma (Pagès et al., 2010). In the first case, a whole brain radiotherapy was associated with chemotherapy (fotemustin) during the second and third trimesters; in the second case, brain gamma knife stereotactic radiosurgery was performed as a single treatment at 23 WA for 3 cerebral metastases. The fetal dose was estimated for only the 2^{nth} case with thermoluminescent dosimeters put on epigastrium and in vagina and was between 0,02 and 0,04 Gy for a maximum tumour dose of 20 Gy; the fetal exposure was less than 0,1 Gy, a dose below the deterministic threshold. No morphological abnormalities were observed in the two newborns with a follow-up of respectively 23 and 2 months. Several case series (Yu et al., 2003; Magné et al., 2001) have reported the birth of healthy babies from mothers who received radiotherapy for cerebral metastases.

5.3.4 Chemotherapy

Malignancy during pregnancy poses special challenges because of the conflict between the need to optimally treat the mother, while minimising risk to both mother and fœtus. The mother should be properly counselled so that she can reach an informed decision. The risks incurred by the foetus differ according to the moment of the exposure: indeed, the instatement of chemotherapy in the first trimester of pregnancy entails the risk of foetal death *in utero*, spontaneous miscarriage and congenital malformation (teratogenicity). In the course of the second and third trimesters, the risks are different, mainly prematurity and intra-uterine growth retardation. The risk incurred also varies with the molecule used. Fotemustine and dacarbazine are two molecules belonging to the alkylating agent group, frequently used in the treatment of metastatic melanoma. Their use in pregnant women has been the subject of only a few publications in the literature. Since the 1960s, 37 cases of administration of dacarbazine to pregnant women have been reported, of which 8

concerned the first trimester (Table 3). Two neonates exposed during the first trimester presented congenital malformations: hypoplasia of the left thumb and bilateral agenesis of the metacarpals in the case reported by Dilek et al; microphthalmia and severe hypermetropia in the case reported by Li et al. (Table 3). The imputability of dacarbazine in these malformations was nevertheless hypothetical, since the drug had been administered in both cases in association with other cytotoxic agents. Among the 29 infants exposed *in utero* to dacarbazine in the second and third trimesters of pregnancy (Table 4), no congenital malformation was noted and nearly 50% were born prematurely, which is a significantly high proportion in comparison to prematurity rates in France in 2003, of the order of 7% (Bourillon, 2005). Nevertheless, we can not exclude that the alterated general health status of the mother take an important part in the high rate of prematurity observed. Likewise, in the general population, spontaneous abortion ranges from 10 to 20% while 3-4% of live birth suffers congenital anomalies (New York State Department of Health. Congenital Malformation Registry 1995 – annual Report); it is important to consider this information in the interpretation of the outcome of pregnant cancer patients treated during gestation.

Authors	Number of cases reported	Type of maternal cancer	Chemo-therapy	Term at delivery (WA)	Existence of congenital malformation	Infant outcome (follow-up)
Zemlickis et al., 1992	1	Melanoma	Dacarbazine	TA	NA	NA
Avilès et al., 1991	4	Hodgkin's disease	ABVD	37 38 40 40	No	All alive (4-14 years)
Dilek et al., 2006	2	Hodgkin's disease	ABVD	NR	Yes, 1 case hypoplasia of the left thumb and bilateral agenesis of the metacarpals	NR
Li et al., 2007	1	Melanoma	Cisplatin, carmustin, dacarbazine, tamoxifen	34	Micro-phthalmia, hypermetropia	Alive (1 year)

Abbreviations : ABVD : adriamycin, bleomycin, vinblastine, dacarbazine, WA : weeks of amenorrhea, TA: therapeutic abortion, NA: not applicable, NR: not reported

Table 3. Cases reported of administration of Dacarbazine during the first trimester of pregnancy.

The series published by Avilès et al. provides a relatively long follow-up of children exposed *in utero* to dacarbazine administered with other chemotherapy agents: the median follow-up was 9 years (range 3-16 years). The development of these 10 children, in terms of stature and weight, was considered normal in comparison with a control group of the same age and from the same socio-cultural environment. Likewise, no case of delayed psycho-motor development was observed: all the children entered normal schooling when the time came; the results of IQ tests showed no significant differences with the control group.

Authors	Number of cases reported	Type of maternal cancer	Chemotherapy received	Term at delivery (WA)	IUGR	Infant outcome (follow-up)
Avilès et al., 1991	6	Hodgkin's disease	ABVD	38 34 35 37 38 36	No	All healthy. (median follow-up: 9 y)
Cardonick et al., 2004	9	Hodgkin's disease	ABVD	NR	No	Healthy (median follow-up:5 y)
Lishner et al.1992	4	Hodgkin's disease	ABVD	NR	No	NR
Hill et al., 1974	1	Melanoma	Dacarbazine	NR	No	Healthy (3 y)
Toussi et al., 1974	1	Melanoma	Dacarbazine	32	No	Healthy (3 y)
Harkin et al.,1990	1	Melanoma	Dacarbazine	38	No	Healthy (4 y)
DiPaola et al.,1997	1	Melanoma	Cisplatin, dacarbazine, carmustin, tamoxifen	30	No	Healthy (1 y)
Dilek et al., 2006	1	Hodgkin's disease	ABVD	IUFD (36)	NR	NA
Jonsthon et al., 1998	1	Melanoma	Dacarbazine	31	No	Healthy (1 y)
Pagès et al., 2010	3	Melanoma	Dacarbazine	36 37 26	Yes (n=1)	Healthy (median follow-up: 8 m)
Gottschalk et al., 2009	1	Melanoma	Dacarbazine, cisplatin	28	Yes	NR

Abbreviations: ABVD: adriamycin, bleomycin, vinblastine, dacarbazine, IUFD : intra-uterine foetal death, IUGR : intra-uterine growth retardation, NR : not reported, NA : not applicable, Y: years, M: months

Table 4. Cases reported of administration of Dacarbazine during second and third trimesters of pregnancy.

Thus, present knowledge concerning the use of dacarbazine in pregnant women is sparse, based on isolated clinical cases or small series, and in the majority of cases dacarbazine was administered as part of poly-chemotherapy. All these elements make it difficult to determine the risk associated specifically with the use of this molecule.

Regarding fotemustin, we reported a case of administration in the second and third trimesters of pregnancy in a patient aged 28 followed for a stage IVM1C melanoma, together with whole brain radiotherapy. On account of a marked degradation in the general

condition of the mother and significant intra-uterine growth retardation, the delivery was induced at 30 WA, giving birth to a female child weighing 820 grammes, with no notable malformation or sign suggesting metastatic localisations; the placenta was free of metastases; at 23 months, the child was alive and well.
In conclusion, dacarbazine and fotemustin should not be electively started during the first trimester of pregnancy, but these drugs can be administered during the second and third trimesters with reasonable safety, although there is an increased risk of stillbirth, growth retardation and premature delivery. The follow-up of these children is an important issue. Indeed, in the literature, the follow-up of children exposed *in utero* to chemotherapy is often too short and therefore the risk of secondary malignancy is likely to be underestimated.

6. Conclusion

The diagnosis of melanoma in the course of pregnancy is not an exceptional situation, and the provision of treatment in the case of advanced melanoma in pregnant women raises certain issues that are at once medical, ethical and philosophical. While in previous decades, pregnancy in patients with cancer was discouraged, currently such pregnancies are treated with more optimism; however, a right balance has to be found between the risks for the mother and those for the foetus. This particular situation requires a multidisciplinary approach involving, among others, surgeons, oncologists, paediatricians, gynaecologists, obstetrician and radiotherapists. Despite the lack of published guidelines, most of the conventional treatment strategies appear to be feasible in the second and third trimesters of pregnancy with appropriate protection measures. International collaboration is required in order to collect data on a sufficient numbers of births among women with cancer in order to obtain more precise risk estimates for adverse infant outcomes. A long-term follow-up of these children born to women with cancer should also be established and documented.
The information given to the mother and her family should be clear and honest, and in line with present scientific knowledge, not only concerning the possible damaging effects on the fœtus of any given substance, but also on the possible transmission of cancer to the child, in particular in case of advanced maternal melanoma. The prognosis of the disease, and the possibility that the child might have to grow up without his mother, should also be brought up.
The arrival of innovatory therapies in the area of advanced melanoma, such as immunotherapy with anti-CTLA4 antibodies (ipilimumab) or targeted therapies (anti BRAF, anti MEK) constitute a revolution in the care of these patients and raise genuine hopes in terms of prognosis. If these hopes are confirmed, dealing with these drugs during pregnancy will be our tomorrow challenge.

7. References

Alexander A, Samlowski W, Grossman D, *et al*: Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *J Clin Oncol*, 2003, vol. 21, pp. 2179-2186

Alexander A. Vulvar melanoma: diffuse melanosis and metastasis to the placenta. *J Am Acad Dermatol*, 2004, vol. 50, n° 2, pp. 293-298

Altman JF, Lowe L, Redman B, *et al.* Placental metastasis of maternal melanoma. *J Am Acad Dermatol*, 2003, vol. 49, n°6, pp. 1150-1153

Anderson JF, Kent S, Machin GA. Maternal malignant melanoma with placental metastasis: a case report with literature review. *Pediatr Pathol*, 1989, vol. 9, pp. 35-42

Antypas C, Sandilos P, Kouvaris J, *et al.* Fetal dose evaluation during breast cancer radiotherapy. *Int J Radiat Oncol Biol Phys*, 1998, vol.40, n°4, pp. 995-999

Aronsson S: A case of transplacental tumor metastasis. *Acta Pediatr Scand*, 1963, vol. 52, pp. 123-134

Arora R, Robinson WA. Breast metastases from malignant melanoma. *J Surg Oncol,* 1992, vol. 50, n°1, pp. 27-29

Avilès A, Diaz-Maqueo JC, Talavera A, *et al*. Growth and development of children of mothers treated with chemotherapy during pregnancy: current status of 43 children. *Am J Hematol*, 1991, vol. 36, pp. 243-248

Azim HA, Pavlidis N, Peccatori FA. Treatment of tye pregnant mother with cancer : a systematic review on the use of cytotixic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: Hematological tumors. *Cancer Treat Rev* 2010, vol 36, pp. 110-121

Baergen R, Johnson D, Moore T, *et al:* Maternal melanoma metastatic to the placenta. *Arch Pathol Lab Med*, 1997, vol. 121, pp. 508-511

Balch CM, Buzaid AC, Soong SJ, *et al*. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*, 2001, vol. 19, pp. 3635-3648

Bourrillon A. Pédiatrie. 3e éd. Paris : Masson, 2005. 880p. 978-2-294-01947-0

Brodsky I, Baren M, Kahn SB, et al: Metastatic melanoma malignant from mother to the fetus. *Cancer,* 1965, vol. 18, pp. 1048-1054

Brossard J, Abish S, Bernstein ML *et al*. Maternal malignancy involving the products of conception. *Am J Pediatr Hematol Oncol*, 1994, vol. 16, pp. 380-383

Byrd BF, McGanity WJ. The effect of pregnancy on the clinical course of malignant melanoma. *South Med J,* 1954, vol. 47, pp. 196-200

Campbell FA: Magnetic resonance imaging for stage IV melanoma during pregnancy. *Arch Dermatol*, 2006, vol. 142, pp. 393

Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol*, 2004, vol. 5, pp. 283-291

Cavell B: Transplacental metastasis of malignant melanoma: Report of a case. *Acta Paediatr Suppl*, 1963, vol. 146, pp. 37-40

Chen M.M, Coakley F.V, Kaimal A, Laros Jr R.K. Guidelines for Computed Tomography and Magnetic Resonance Imaging use during pregnancy and lactation. *Obstet Gynecol* 2008, vol 112, pp. 333-40

Cranmer LD, Jeter JM, Morgan SS et al. Whole brain radiotherapy in melanoma: an open question. *Lancet Oncol* 2010, vol 11, n°1, pp. 13

Dargeon HW, Eversole JW, Del Duca V: Malignant melanoma in an infant. *Cancer,* 1950, vol. 3, pp. 299-306

Daryanani D, Plukker JT, De Hullu JA, *et al.* Pregnancy and early stage melanoma. *Cancer*, 2003, vol.97, pp.2248-2253

Dekaban S. Abnormalities in children exposed to X-radiation during human various stages of gestation. I. Tentative timetable of radiation injury to the human fetus. *Int J Nucl Med*, 1968, vol. 9, pp. 471-477

De Santis M, Straface G, Cavaliere AF *et al*. Gadolinium periconceptionnal exposure: pregnancy and neonatal outcome. *Acta Obstet Gynecol Scand*, 2007, vol. 86, n°1, pp. 99-101

Dessolle L, Dalmon C, Roche B, et al: Métastases placentaires de cancers maternels: revue de la littérature. *J Gynecol Obstet Biol Reprod,* 2007, vol. 36, pp. 344-353

Dilek I, Topcu N, Demir C, *et al.* Hematological malignancy and pregnancy: a single-institution experience of 21 cases. *Clin Lab. Haem*, 2006, vol. 28, pp. 170-176

Dillman RO, Vandermolen LA, Barth NM *et al.* Malignant melanoma and pregnancy: ten questions. *West J Med*, 1996, vol. 164, pp. 156-161

Dipaola RS, Goodin S, Ratzell M *et al.* Chemotherapy for metastatic melanoma during pregnancy. *Gynecol Oncol,* 1997, vol. 66, pp. 526-530

Egberts F, Lischner S, Russo P et al. Diagnostic and management procedures for management of melanoma during pregnancy; risk for the fetus? *J Dtsch Dermatol Ges*.2006, vol 4, pp. 717-720

Ferreira CM, Maceira JM, Coelho JM: Melanoma and pregnancy with placental metastases: Report of a case. *Am J Dermatopathol*, 1998, vol. 20, pp. 403-407

Freedman WL, McMahon FJ. Placental metastasis: review of the literature and report of a case of malignant melanoma. *Obstet Gynecol*, 1960, vol. 16, pp. 550-560

Fujinaga M, Mazze RI. Reproductive and teratogenic effects of lidocaine in Sprague-Dawley rats. *Anesthesiology* 1986, vol 65, pp. 626-32

Gentilini O, Cremonesi M, Trifiro G *et al*. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol*, 2004, vol. 15, pp. 1348-1351

Gillis H, Mortel R, McGavran MH. Maternal malignant melanoma metastatic to the product of conception. *Gynecol Oncol,* 1976, vol. 4, pp. 38-42

Gormley DE. Cutaneous surgery and the pregnant patient. *J Am Acad Dermatol* 1990, vol 23, pp. 269-79

Gottschalk N, Jacobs V.R, Hein R et al. Advanced metastatic melanoma during pregnancy: a multidisciplinary challenge. *Onkologie* 2009, vol 32, pp 748-751

Gottron H, Gertler W: Zur frage des ubertritts von melanogen der mutter au den saugling uber die muttermilch. *Arch Dermatol Syph*, 1940, vol. 181, pp. 91-98

Grange F. Epidémiologie du mélanome cutané: données descriptives en France et en Europe. *Ann Dermatol Venereol*, 2005, vol. 132, pp. 975-982

Guidelines for diagnostic imaging during pregnancy. ACOG Committee Opinion No. 299. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2004, vol 104, pp. 647-651

Gupta A, Driscoll MS. Do hormones influence melanoma? Facts and controversies. *Clin Dermatol* 2010, vol 28, pp.287-292

Harkin KP, Drumm JE, O'Brien P, *et al*. Metastatic melanoma in pregnancy. *Ir Med J*, 1990, vol. 83, n° 3, pp. 116-117

Hill GJ, Ruess R, Berris R *et al*. Chemotherapy of malignant melanoma with dimethyl triazeno imidazole carboxamide and nitrosourea derivatives. *Ann Surg*, 1974, vol. 180, n° 2, pp. 167-174

Holcomb BW, Thigpen JT, Puckett JF *et al*. Generalized melanosis complicating disseminated malignant melanoma in pregnancy: a case report. *Cancer,* 1975, vol. 35, pp. 1459-1464

Holland E: A case of transplacental metastasis of malignant melanoma from mother to foetus. *J Obstet Gynaecol Br Emp*, 1949, vol. 56, pp. 529-536

Jonsthon SR, Broadley K, Henson G *et al*. Management of metastatic melanoma during pregnancy. *Br Med J,* 1998, vol. 316, pp. 848-849

Kal HB, Struikmans H: Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol,* 2005, vol. 6, pp. 328-333

Kanal E, Barkovich AJ, Bell C et al. ACR guidance document for safe MR pratices: 2007. *Am J Roentgenol* 2007, vol 188, pp. 1447-74

Kirkwood JM, Strawderman MH, Ernstoff MS et al. Interferon alfa-2b adjuvant therapy of high risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol*.1996, vol 14, n°7, pp.17-

Koomen ER, Joosse A, Herings R.M.C, Casparie M.K, Guchelaar H.J δ Nijsten T. Estrogens, oral contraceptives and hormonal replacement therapy increase the incidence of cutaneous melanoma: a population-based case-control study. *Ann Oncol* 2009, vol 20, pp. 358-364

Kuczkowski KM. Nonobstetric surgery during pregnancy: what are the risks of anesthesia? *Obstet Gynecol Surv*, 2004, vol. 59, n° 1, pp. 52-56

Langagergaard V. Birth outcome in women with breast cancer, cutaneous malignant melanoma, or Hodgkin's disease: a review. *Clinical Epidemiology*, 2011, vol.3, pp. 7-19

Lazarus E. 2007 Use of radiological examinations in pregnant women: a ten-year review 1997-2006. Radiological Society of North America Scientific Assembly and Annual Meeting p. 436 Chicago

Lens MB, Rosdahl I, Ahlbom A, *et al.* Effect of pregnancy on survival in women with cutaneous malignant melanoma. *J Clin Oncol*, 2004, vol. 22, pp.4369-4375

Li RHW, Tam WH, Cheung PN, *et al.* Microphtalmos associated with Darmouth combination chemotherapy in pregnancy. *J Reprod Med*, 2007, vol.52, pp. 575-576

Lin SP, Brown JJ. MR Contrast Agents: physical and pharmacologic basics. *J Magn Reson Imaging*, 2007, vol. 25, pp. 884-899

Lishner M, Zemlickis P, Degendorfer T, *et al.* Maternal and foetal outcome following Hodgkin's disease in pregnancy. *Br. J Cancer*, 1992, vol. 65, pp. 114-117

Looi LM, Wang F; Malignant melanoma metastases in chorionic villi: a case report. *Malays J Pathol*, 1979, vol. 2, p. 73-75

Luis SA, Christie DRH, Kaminski A, Kenny L, Peres MH. Pregnancy and radiotherapy : management options for minimising risk, case series and comprehensive literature review. *J Med Imaging Radiat Oncol* 2009, vol 53, pp. 559-568

MacKie RM, Bufalino R, Morabito A, *et al.* Lack of effect of pregnancy on outcome of melanoma. *Lancet,* 1991, vol.337, pp.653-655

Magné M, Marcié S, Pignol JP, *et al.* Radiotherapy for a solitary brain metastasis during pregnancy: a method for reducing fetal dose. *Br J Radiol*, 2001, vol.74, n°883, pp.638-641

Marcos HB, Semelka RC *et al.* Normal placenta: gadolinium-enhanced dynamic MR imaging. *Radiology,* 1997, vol. 205, pp. 493-496

Markus N. Gleichzeitige entwicklung melanosarcoma ovarii und carcinoma hep der schwangerschaft, eklampsie, placentarmetastazen. *Arch F Gynakol*, 1918, vol.92, pp.659-678

Marsh RD, Chu NM. Placental metastasis from primary ocular melanoma: a case report. *Am J Obstet Gynecol*, 1996, vol. 174, pp. 1654-1655

Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. *Am J Obstet Gynecol*, 1989, vol. 161, n° 5, pp. 1178-85

McManammy DS, Moss ALH, Pocock PV, *et al.* Melanoma and pregnancy: a long- term follow-up. *Br J Obstet Gynecol*, 1989, vol.96, pp.1419-1423

Merkus JM, Teepen JL. The indispensable anamnesis: in-vitro fertilization in a woman under treatment for melanoma. *Ned Tijdschr Geneeskd*, 1998, vol. 142, pp. 2073-2075

Mesquita MM, Pestana A, Mota A. Successful pregnany occurring with interferon alpha therapy in chronic myleoid leukemia; *Acta Obstet Gynecol Scand* 2005, vol 84, pp. 300-1

Moller D, Ipsen L, Asschendeldt P. Fatal course of malignant melanoma during pregnancy with dissemination to the product of conception. *Acta Obstet Gynecol Scand,* 1986, vol. 65, pp. 501-502

Mondi MM, Cuenca RE, Ollila DW, *et al.* Sentinel lymph node biopsy during pregnancy: initial clinical experience. *Ann Surg Oncol*, 2007, vol. 14, n°1, pp. 218-221

Moran B.J, Yano H, Zahir N, Farquaharson M. Conflicting priorities in surgical intervention for cancer in pregnancy. *Lancet Oncol* 2007, vol 8, pp. 536-44

Naggara O, Brami-Zylberberg F, Rodrigo S, *et al*. Imaging of intracranial metastases in adults. *J Radiol*, 2006, vol. 87, pp. 792-806

New York State Department of Health. Congenital Malformation Registry 1995- annual report.

Nicklas AH, Baker ME: Imaging strategies in the pregnant cancer patient. *Semin Oncol*, 2000, vol. 27, n°6, pp. 623-32

Oduncu F.S, Phil M.A, Kimmig R, *et al:* Cancer in pregnancy: maternal-fetal conflict. *J Cancer Res Clin Oncol*, 2003, vol. 129, pp.133-146

O'Meara AT, Cress R, Xing G, *et al.* Malignant melanoma in pregnancy: a population- based evaluation. *Cancer*, *2005*, vol.103, pp.1217-1226

Otake M, Schull WJ, Lee S. Treshold for radiation related severe mental retardation in prenatally exposed A bomb survivors: a re-analysis. *Int J Radiat Biol,* 1996, vol. 70, n° 6, pp. 755-763

Otake M, Schull W. Radiation-related small head sizes among prenatally exposed A-bomb survivors. *Int J Radiat Oncol Biol Phys*, 1992, vol. 63, pp. 255-270

Pagès C, Robert C, Thomas L, et al.. Management and outcome of metastatic melanoma during pregnancy.*Br J Dermatol;* 2010, vol 162, pp.274-281

Patel AJ, Suki D, Hatoboqu MA et al. Factors influencing the risk of local recurrence after resection of a single brain metastasis. *J Neurosurg* 2010, vol 113, n°2, pp. 181-9

Pavlidis NA. Coexistence of pregnancy and malignancy. *Oncologist* 2002, vol 7, pp. 279-87

Pennoyer JW, Grin CM, Driscoll *et al.* Changes in size of melanocytic nevi during pregnancy. *J Am Acad Dermatol*, 1997, vol. 36, pp.378-82

Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. *Eur J Cancer*, 2006, vol.42, pp. 126-140

Pentheroudakis et al. Cancer, fertility and pregnancy : ESMO clinical practice guidelines fir diagnosis, treatment and follow-up. *Ann Oncol* 2010, vol 21, n°5, pp. 266-273

Pruthi S, Haakenson C, Brost B;C et al. Pharmacokinetics of methylene blue dye for lymphatic mapping in breast cancer - implications for use in pregnancy. *Am J Surg* 2011, vol 201, n°1, pp.70-5

Regierer AC, Schulz CO, Kuehnhardt D et al. Interferon alpha therapy for chronic myeloid leukemia during pregnancy. *Am J Hematol* 2006, vol 81, pp. 149-150

Reintgen DS, McCarty KS, Vollmer R, *et al*. Malignant melanoma and pregnancy. *Cancer,* 1985, vol.55, pp.1340-1344

Reynolds AG. Placental metastasis from malignant melanoma: report of a case. *Obstet gynecol*, 1955, vol. 6, pp. 205-209

Richards K.A, Stastko T. Dermatologic surgery and the pregnant patient. *Dermatol Surg* 2002, vol 28, n°3, pp. 248-56

Rosen MA. Management of anesthesia for the pregnant surgical patient. *Anesthesiology*, 1999, vol. 91, n° 4, pp. 1159-63

Roux C, Horvath C, Dupuis R. Effects of pre-implantation lowdose radiation on rat embryos. *Health Phys*, 1983, vol. 45, n°5, pp.993-999

Russell P, Laverty CR. Malignant melanoma metastases in the placenta: a case report. *Pathology,* 1977, vol. 9, pp. 251-255

Shiu MH, Schottenfeld D, Maclean B, Fortner JG. Adverse effect of pregnancy on melanoma: a reappraisal. *Cancer,* 1976, vol 37, n°1, pp. 181-187

Slingluff CL, Reintgen DS, Vollmer RT, *et al.* Malignant melanoma arising during pregnancy: a study of 100 patients. *Ann Surg,* 1990, vol.211, pp.552-559

Smythe AR, Underwood PB, Kreutner A. Metastatic placental tumors. *Am J Obstet Gynecol*, 1976, vol. 125, pp. 1149-1151

Sokol RJ, Hutchinson P, Cowan D *et al.* Amelanotic melanoma metastatic to the placenta. *Am J Obstet Gynecol*, 1976, vol. 124, pp. 431-432

Stensheim H, Moller B, Van Dijk T, Fossa SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study, *J Clin Oncol*, 2009, vol 27, n°1, pp. 45-51

Stephenson HE Jr, Terry CW, Lukens JN *et al.* Immunologic factors in human melanoma "metastatic" to the products of gestation. *Surgery,* 1971, vol. 69, pp. 515-522

Stovall M, Blackwell R.C, Cundiff J et al. Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group. *Med Phys,* 1995, vol. 22, n° 1, pp. 63-82

Streffer C, Shore R, Konermann G, *et al*. Biological effects after prenatal irradiation (embryo and fetus). A report of the International Commission on Radiological Protection. *Ann ICRP*, 2003, vol. 33, n°1-2, pp. 5-206

Thompson BH, Stanford W. MR imaging of pulmonary and mediastinal malignancies. *Magn Reson Imaging Clin N Am*, 2000, vol. 8, pp. 729-739

Toussi T, Blais M, Langevin P, et al. Mélanome métastatique traité chez une femme enceinte : implications pré et postnatales. *Union Med Can*, 1974, vol. 103, pp. 1968-1973

Trumble ER, Smith RM, Pearl G, et al: Transplacental transmission of metastatic melanoma to the posterior fossa. *J Neurosurg (Pediatrics 2),* 2005, vol. 103, pp.191-193

Valenzano Menada M, Moioli M, Garaventa A, Nozza P, Foppiano M, Trimarchi N, Fulcheri E. Spontaneous regression of transplacental metastases from maternal melanoma in

a newborn: case report and review of the literature. *Melanoma Research* 2010, vol 20, pp. 443-449

Van der Horst M, Winther JF, Olsen JH. Cancer incidence in the age range 0-34 years: historical and natural status in Denmark. *International Journal of Cancer*, 2006, vol 118, n°11, pp. 2816-2826

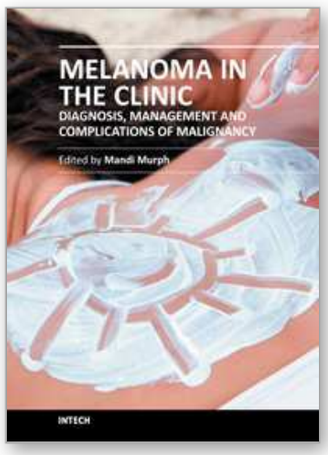
Webb JA, Thomsen H, Morcos SK *et al.* The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol*, 2005, vol. 15, pp. 1234-1240

Weber FP, Schwarz E, Hellenschmied R: Spontaneous inoculation of melanotic sarcoma from mother to foetus. *Br Med J,* 1930, vol. 1, pp.537-539

Wong JH, Styerns EE, Kopald KH, *et al.* Prognostic significance of pregnancy in stage I melanoma. *Arch Surg,* 1989, vol.124, pp.1227-1231

Yu C, Jozsef G, Apuzzo ML, *et al.* Fetal radiation doses for model C gamma knife radiosurgery. *Neurosurgery,* 2003, vol. 52, n°3, pp. 687-693

Zemlickis D, Lishner M, Degendorfer P, *et al.* Fetal outcome after in utero exposure to cancer chemotherapy. *Arch Intern Med*, 1992, vol. 152, pp. 573-576



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This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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