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Review

Melanoma and pregnancy: Current treatment trends and future potentials

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Abstract

Malignant melanoma is one of the most frequent cancers that relate to pregnancy. Therapeutic approach of malignant melanoma during pregnancy is a challenge that the modern obstetrician – gynecologist has to face, in collaboration with medical doctors of other specialties, in specially organized medical centers. Surgical treatment in combination with radiotherapy and chemotherapy depend on the stage of the disease and the gestational age. In the current review, based on the current data, a brief literature review of the malignant melanoma during pregnancy is attempted, mostly related to the current available therapeutic options, the proper knowledge of which contributes decisively to the best possible prognostic outcome.

Keywords: Malignant melanoma, Pregnancy, Management, Surgical treatment, Complementary treatment

INTRODUCTION

Diagnosing cancer during pregnancy is not a common incident. Cancer to pregnant women show up in a ratio of one to 1000 pregnancies (Pariyar et al, 2012). More current data demonstrated that cancer's appearance during pregnancy is even more frequent, and is calculated to be 145.4 cases in every 100000 pregnancies (Lee et al, 2013). Cancer related to pregnancy have increased in number during the past years, an increase that is mainly related to the increase of the reproduction age of modern women. Also, the testing that nowadays a pregnant woman goes through during pregnancy greatly increases the possibility of cancer diagnosis. Malignancies that appear more frequently during pregnancy arb rest cancer, malignancies of the reproductive system, thyroid gland cancer, leukemia, lymphoma and malignant melanoma (Lee et al, 2012).

Malignant melanoma develops from melanocytes that produce melanin. Melanocytes derive from melanoblasts which during embryonic development immigrate from the posterior part of the ganglion crest to the eye, the mucosas, the meninges, the inner ear, the dental cavity, the mesentery and of course the skin, that though can't be detected after birth. Melanoma in most cases develops at the skin (91.2%). In a small percentage 5.2% melanoma occurs at the eyes, while in a 1.3% of the cases at the mucosa (Chang et al, 1998). Development of a benign melanocyte towards malignancy is a complicated and not a fully researched procedure. This procedure is a combination of interactions between environmental factors, accumulated genetical mutations, activation of oncogenes, disablement of tumor suppressor genes and damages during DNA repair procedure (Uribe et al, 2005; Pho et al, 2006). In general, epidermal phenotype of a person, the presence of atypical moles (dysplastic nevi), family history of melanoma and the presence of genetic syndromes, like xeroderma pigmentosum or psoriasis are well known risk factors for developing the disease (Kraemer and DiGiovanna, 2003; Ferrone et al, 2005; Lin and Fisher, 2007; Olsen et al, 2010).

Malignant melanoma is the most severe type of skin cancer (Abbas et al, 2014). Melanomas have an increased prevalence in most Caucasian populations the past 30 years ((Linos et al, 2009; Erikson and Driscoll, 2010). The disease is calculated to be 1-4% of all malignant tumors in humans and is responsible for the 80% of the mortality of skin cancer. Caucasian race have the biggest skin melanoma prevalence, while mucosal melanoma hase a bigger prevalence in Negroid and Asiatic race (Karim – Kos et al, 2008). In general, the frequency of the disease's prevalence varies depending

on the geographical distribution of the population. While in Australia and New Zeland the disease is calculated to have the biggest frequency 40-60 cases in 100000 of general population per year, in the United States of America the prevalence is downsized to 18 cases in 100000 of population per year. In Europe melanomas prevalence is even smaller and is calculated to be 10-15 cases in 100000 of total population per year (Garbe and Leiter, 2009).

Malignant Melanoma during Pregnanacy

Melanoma is a malignant tumor that derives from melanocytes of dermoepidermal junction. It is one of the most frequent malignant neoplasms that manifest during pregnancy. The neoplasia appearance on pregnant women is calculated to be one in every 1000 pregnancies and is increasing drastically during the last years. Also, melanoma is the most frequent pregnancy-occurring neoplasia that can affect the fetus through placental metastases (Altman et al, 2003; Perret – Court et al, 2010). So even though placental metastases are rare, melanoma is the most frequent neoplasia that metastasizes at placental tissue in a percentage of around 30% of pregnancy affecting tumors at fetuses. Most published studies related to melanoma during pregnancy focus on the mother. Some studies have researched the risk of melanoma being transmitted from the mother to the fetus and have calculated that the mortality risk on newborns being born by mothers with placenta infection is about 25%. Melanoma's ability to metastasize compared to other neoplasias for the placenta and the fetus have not been fully explained yet, although it is estimated that there is something special when it comes to melanoma's cells and their ability to metastasize (Richardson et al, 2002).

Malignant melanoma in pregnant women is more frequent than breast cancer and ovarian cancer. Breast cancer during pregnancy is estimated to affect about 1:3000 to 1:10000 women, malignant melanoma affects 1:1000 to 1:10000 pregnant women and ovarian cancer is estimated to affect 1:10000 to 1:100000 pregnancies (Pavlidis, 2002; Alexander et al, 2003; Pereg et al, 2008; Hoellen et al, 2012). Most current data demonstrated that the frequency of ovarian cancer during pregnancy is greater than that, and is estimated about 2.8 to 8.5 cases in every 100000 pregnancies (O´Meara et al, 2005). Other researchers estimate that malignant melanomas consist about the 8% of all the malignant neoplasms that appear during pregnancy (Gottschalk et al, 2009).

Melanomas affect mostly young women of reproductional age and seem to relate to the number of total pregnancies a woman had. Specifically, recent studies showed that multigravidas have a reduced risk of developing melanoma compared to childless women (Lens and Betaille, 2008; Gandini et al, 2011).

Therapeutical Approach

There are not clear guidelines for confronting malignant melanoma on pregnant women. The investigation of a pregnant woman with a suspicious dark colored skin lesions has to be the same with a non pregnant woman. Generally, saving the mother's life, sufficient therapeutic approach of the treatable malignancies, effort to protect the fetus and newborn from the damaging effects of the antineoplastic treatment and the effort to retain undamaged the female reproductive system have to be the objectives of the current proposed available therapeutic approach of cancer during pregnancy. Like in any other high risk pregnancies, pregnant women with malignant melanoma have to be frequently monitored in specially organized medical centers from a specialized team of physicians that has to include an obstetrician/gynecologist, a surgeon, an oncologist, a diagnostic radiologist and a neonatologist. The frequent ultrasound evaluation of fetus growth, the evaluation of the amniotic fluid volume (AFI – Amniotic Fluid Index) in regular basis, the evaluation of blood flow through the omphalic vessels with Doppler sonography and performing fetal non-stress tests (NST- Non Stress Test) after the 28th gestational week until the end of pregnancy is highly important for every pregnant woman having malignant melanoma. Therefore, the basic principles of treatment of malignant melanomas during pregnancy consist of frequent monitoring of the pregnant woman, constant evaluation of the fetal status, surgical treatment of the disease, chemotherapy and actinotherapy, as shown on Table 1.

Table 1. Treatment options of approach of malignant melanoma during pregnancy

- Systematic monitoring of the pregnant woman
- Constant evaluation of the fetus
  - -biometry
  - -amniotic fluid volume measurement
  - -Doppler of omphalic vessels
  - -NST
- Surgical treatment
  - -wide excision
  - -lymphadenectomy
- Chemotherapy
  - -dacarbazine
  - -bleomycine
  - -vincristine
  - -lomoustin
- Immunotherapy
- Radiotherapy
- Targeted therapy
- Local hyperthermia
- Growth factors
- Vaccination
- Pregnancy termination

Surgical treatment

The initial appropriate current therapeutical approach of malignant melanoma during pregnancy is the surgical treatment. Surgical treatment continues to be the basis of malignant melanoma's treatment. Changes of the clinical characteristics of a mole during pregnancy can't in any circumstances be considered normal. In that case, an immediate biopsy of the skin lesion with local anesthesia is appropriate. Even though many surgical technics have been proposed, the excision biopsy with supplementary excision of one to two millimeters of healthy tissue around the lesion, is the method of choice in the diagnostic approach of skin lesions suspicious to me melanomas. This method allows total removal of the lesion and in the same time offers valuable information about disease's staging (Balch et al, 2009. The local anesthetic that is more commonly used is lidocaine, in which is possible to add epinephrine, in order to add an hemostatic effect and to extend the duration of lidocaine's effect on the surgical field (Gormley, 1990; Lawrence, 1996).

The surgical procedure is able to be performed in any trimester of pregnancy, although it is considered preferable for the first trimester to be avoided, in ordr to avoid the risk of fetal loss. The type of surgical procedure depends on the disease's stage and the type of the skin lesion. In cases of big sized lesions located on the patient's face, or in melanotic freckle lesions (lentigo maligna) that are located on limbs or on mucous membranes, diagnostic or partial biopsy may be performed in order to confirm the diagnosis. Partial biopsies are more difficult to be histological evaluated and there is always the risk of the deepest part of the tumor not being excised. Even so, big clinical trials have shown that patients that underwent partial biopsy or not radical excision for treating malignant melanoma did not have a worse prognosis compared to the prognoses of patients that had radical excision of the lesion (Garbe et al, 2012; Garbe et al, 2016).

For first and second degree melanoma a wide surgical excision of the skin lesion and Sentinel Lymph Node Biopsy (SLNB) is appropriate. Proper surgical treatment of the melanoma should include the excision of both the skin lesion and the subcutaneous fat tissue, without removing the subject muscle aponeurosis. This way healthy excision boundaries are ensured and at the same time local tumor recurrence is avoided (Sladden et al, 2009). Wider surgical excisions have no indication, because its estimated that they don't seem to improve the total survival rate of the patients, because both remote metastases and local recurrences relate mainly to the biology of the tumor (Gillgren et al, 2011). For the cases that a wider excision of the melanoma is indicated bigger portions of local anesthetics are required. A mixture of lidocaine – epinephrine is proposerad to be used with caution, using an epinephrine concentration os 2.5 to 5.0 μg/ml (Rosenberg et al, 2004). In some other cases the excision of the lesion is possible to be considered necessary to be done under general anesthesia (Hoekstra, 2008).

Sentinel Lymph Node Biopsy (SLNB) is a valuable tool for disease staging. It aims at evaluating the first draining lymph node of a wider area of local lymph nodes. This technique is appropriate for patients with high risk of tumor dissemination, for which neither clinical examination nor ultrasonography can determine lymph metastases. In cases when the sentinel lymph node biopsy is considered necessary during pregnancy ambiguousness exists about the safety of these methods. In clinical practice the time and way of performing the method depends on the surgeon and the medical center. Usually either a radioactive colloid (technetium 99m - Tc) or isosulfan blue 1% is used, or they can be both used. Some surgeons avoid using radioactive colloids during pregnancy, in order to avoid the exposure of the fetus to radiation ακτινοβολία (Squatrito and Harlow, 1998). Other researchers believe that this dosage of radiation is minimum and so safe for the fetus. Radioactive colloid ca be used alone for the localization of the sentinel lymph node, because the fetus is exposed to a small amount of radiation, which is ment to be neglectable and does not increase the risk for fetal anomalies (Pandit – Taskar et al, 2006).

In the case that the sentinel lymph node is positive – metastases in the sentinel lymph node – a complete lymphadenectomy of that lymph node station is suggested. In the cases where a therapeutic lymphadenectomy is required, its useful that it's not delayed by the pregnancy. Lymphadenectomy of the lateral and posterior cervical lymph nodes, the axillary lymph nodes till level III and the superficial inguinal lymph nodes can be easily performed during pregnancy. The excision of the deep inguinal lymph nodes is rather difficult (Pentheroudakis et al, 2010). In cases when a lymphoscintigram is considered necessary, it is advised to avoid a dosage that exceeds 10MBq and surgical excision should be done within six hours. In this case the fetus is exposed to a radiation equal to six days exposure to environmental radiation (Morton et al, 2006). Finally, on terminally ill pregnant patients an histological exam of the placenta is highly important for tracing of metastatic disease. Even if the frequency of placental metastases is extremely low, their tracing is considered to offer an important benefit in ensuring the best perinatal outcome and in the afterbirth health of the child (Alexander et al, 2003; Shuhaila et al, 2008).

Post-surgery follow-up shoud include physical examination and chest x-ray. Also, a laboratory test determination of the serum levels of alkaline phosphatase (ALP), of γ – GT and of LDH is suggested every 3 to 6 months for the first 2 years, following every 6 months for the next 3 to 5 years and finally after that once a year. In any case of suspicion of illness recurrence, further

investigation is suggested using computerized axial tomography (CT), magnetic resonance imaging (MRI) and scintigraphy using monoclonal antibodies or non-specific tumor-targeting radioactive drugs or/and fluorine – 18 – fluorodeoxyglucose – positron emission tomography (18F – FDG – PET) (Wilke et al, 2006).

Complementary treatment

Chemotherapy, immunotherapy, radiotherapy, local hyperthermia, vaccination and other promising future experimental therapeutic approaches are complementary – subsidiary treatment methods that have at times been suggested to be included in treatments of malignant melanomas after lymphadenectomy. Chemotherapy was the only therapeutic method for the metastatic melanoma, with low success rate results and with no significant effects on survival rates (Sosman, 2016). Even so, there are studies that have evaluated its administration during pregnancy for the metastatic melanoma. Chemotherapy should be delayed for the second or third trimester of pregnancy. Use of chemotherapeutic drugs during the first trimester is associated with significantly increased risk of spontaneous abortion and congenital physical anomalies of the newborn. Among the chemotherapeutic drugs, dacarbazine in combination with other chemotherapeutic factors, like bleomycin, vincristine and lomustine is proven to be the most effective treatment method of metastatic melanoma (Lens and Eisen, 2003; Pagès et al, 2010).

Epidemiological studies referring to congenital anomalies of newborns of women that received dacarbazine during pregnancy do not exist. The only thing that has been published are individual cases, where the use of dacarbazine during second trimester did not cause congenital anomalies to the newborns (Vuoristo et al, 2005; de Haan et al, 2017). Even so, initiation of premature labor, preeclampsia, intra-uterine growth restriction of the fetus and leucopenia of the newborn are included to the possible complications after the use of chemotherapeutic drugs of pregnant women during the second and third trimester of pregnancy (Harkin et al, 1990; Hahn et al, 2006).

Frequently the use of chemotherapeutic drugs should be combined with growth factors that provide haematological support of the patients that undergo chemotherapy for treating cancer (Gwyn, 2005). Also, the indication for administration of complementary immunotherapy with interferon – α (alpha) is relative in the treatment of pregnant women with advanced disease (Egberts et al, 2006). During the last years, treatment of metastatic melanoma has changed dramatically with the introduction of targeted therapy and immunotherapy. The above therapeutic options are currently considered therapy of choice in the treatment algorithm of the disease with encouraging results (Sosman, 2016; John and Cowey, 2015).

Meanwhile, using targeted treatment has not yet been approved for treating malignant melanoma during pregnancy. Administration of targeted therapy (BRAF – Vemurafenid) cannot be safely suggested to pregnant women (Avilés and Neri, 2001). The administration of BRAF V600 (vemurafenid) has been reported in the literature in two cases during pregnancy. In the first case, intrauterine growth restriction was detected which lead to premature cesarean section due to fetal distress, without though any fetal dysmorphias reported (Maleka et al, 2013). In the second case with a woman exposed to BRAF inhibitor (vemurafenib), the patient chose to terminate the pregnancy (de Haan et al, 2017). Immunotherapy and administration of antibody CTLA – 4 (ipilimumab) (IgG1) penetrates the placenta , and in a study that took place on monkeys (Grunewald et al, 2015) an increased frequency of miscarriages, stillborn premature newborns, infant mortalities and dysmorphias in the urogenital tract. Also, the administration of the newer antibodies anti-PD-1 (nivolumab and pembrolizumab) (IgG4) is not considered safe, because the effects that have been described that they have on pregnancies on mice resulted on miscarriage (Wang et al, 2015). Similarly, the administration of vaccines and other similar therapeutic approaches aiming the prevention of malignant melanoma's recurrence are inapplicable during pregnancy (Naylor, 2000; Kirkwood et al, 2006).

Extended lymphatic or exolymphatic or vascular infiltration of the border of the incision are possible indications of complementary radiotherapy. Radiotherapy as complementary method to surgical procedure should be postponed for the period after the labor, because the amount of radiation that is used to treat metastatic melanoma is much higher than those used for diagnostic radiology, resulting in exposure of the fetus to significant risk (Bastiaannet et al, 2005; Daly et al, 2006). Specifically, radiotherapy can have harmful effect on the fetus, like fetal intrauterine growth restriction, congenital dysplasias, intellectual disability and carcinogenesis with radiation doses of 100 - 200 mGy. However, smaller doses can cause cancer development or leukemia during childhood and sterility. In all cases sufficient shielding should be used (Kal and Struikmans, 2005; Fenig et al, 2001). Radiation doses under that limit relate to very low risk of mutation and growth disorders do not appear with frequencies higher that these of the general population (3% – 5%) (Martin et al, 2011).

Complementary radiotherapy during pregnancy can be limited to the lesions that are located on the head and neck, the brain metastases and the compassionate treatment of recurrent or metastatic disease on places other than the central nervous system. Brain metastases (if they are confined) are commonly treated with radiosurgical or neurosurgical excision. Delayng the treatment of brain metastases is not recommended.

Radiotherapy can provide very high doses on very small brain tumors and, with careful treatment planning, treatment of a pregnant patient with minimal fetus exposure is possible (Izycki et al, 2013). De Haan et al. described 3 patients that received radiotherapy during pregnancy. One of the patients received short-term therapy with iodine – 125 for eye melanoma, and the two remaining patient of stage III and IV respectively, received radiotherapy at the axillary space during the second trimester of pregnancy. The estimated fetal receiving dosage of radiation was neglectable in all three cases (de Haan et al, 2017).

Also, the use of techniques, like local hyperthermia regarding the transfer of high doses of chemotherapeutic drugs locally, that has been used both as immediate treatment and as complementary treatment on patients of high risk for recurrence or metastases, are contraindicated during pregnancy (Hoekstra, 2008). Finally, Pregnancy termination on the first trimester, in contradiction to older beliefs concerning its beneficial contribution to the disease's state, nowadays is considered that has not a beneficial effect on the malignant melanoma during pregnancy. In every case though the couple must be informed about the treatment options that are necessary after the first trimester of pregnancy and the risks that these have. Elective pregnancy termination has indication for pregnant women who are in the first trimester of pregnancy and have end-stage disease (Berretta et al, 2012).

CONCLUSIONS

Malignant melanoma is a significant danger for the general population health, with a frequency that is rapidly increasing during the last years. Melanoma consists the most aggressive type of skin cancer. A great amount of cases is considered to originate from atypical moles (dysplastic nevi). Melanoma during pregnancy is a rare, but at the same time important and threatening for the life of the pregnant woman disease, that the modern obstetrician – gynecologist is responsible to treat, in collaboration with the surgeon, the oncologist, the radiotherapist and the neonatologist in specially organized medical centers. Current surgical treatment of pregnant women with malignant melanoma, that nowadays include wide excision of the skin lesion and lymphadenectomy, is considered to be safe during every trimester of pregnancy. Chemotherapy should be delayed until the second or third trimester, while radiotherapy should be performed after labor. The use of targeted therapy is not yet approved as a therapeutic option for malignant melanomas during pregnancy. Pregnancy termination does not seem to improve the prognosis of the disease. Elective pregnancy termination has indication only for pregnant women on first trimester that have end-stage disease.

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