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Melanoma and Pregnancy: Risks, Current, and Forecast

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Abstract

Currently, the term "melanoma associated with pregnancy" is used, implying the inclusion of all clinical observations of melanoma diagnosis during pregnancy and in the first 2 years after delivery. The management of pregnant women with newly diagnosed melanoma is likewise controversial, especially with regard to the management of women with an advanced melanoma. Thrombotic complications are the most common form of paraneoplastic syndrome, which largely determines the prognosis of the disease. The presented chapter is intended to familiarize practical physicians with the complexities that arise in the management of pregnant women with a developing metastatic disease, with questions of the progression of the disease during pregnancy, with the emergence of severe paraneoplastic complications involving secondary thrombophilia, amaranthine endocarditis, and widespread arterial thrombosis. The possibility of using modern antitumor drugs (Zelboraf) is shown. It is emphasized that in the management of such patients, the need for an effective team of specialists of various profiles is especially high: oncologists, obstetrician-gynecologists, surgeons, hematologists, anesthesiologist-resuscitators, and US and magnetic resonance imaging (MRI) diagnostics.

Keywords: melanoma, pregnancy, secondary thrombophilia, paraneoplastic syndrome, vemurafenib

1. Introduction

Melanoma of the skin (*lat. —melanoma, melanoma malignum*) is a malignant tumor that results from neoplastic transformation of melanocytes—cells that produce various variations of melanin pigment [1]. In recent years, there has been an increase in the incidence of skin melanoma in Russia. Between 1998 and 2008, the incidence rate in the Russian Federation was 38.17%, and the standardized morbidity rate rose from 4.04 to 5.46 per 100,000 population. In 2008, the number of new cases of melanoma in the Russian Federation was 7744 people. Mortality from melanoma in the Russian Federation in 2008 was 3159 people and a standardized death rate of 2.23 people per 100,000 population [2]. Approximately one-third of women diagnosed with melanoma are of childbearing age, and a 2015 Swedish population-based cancer registry study found that melanoma was the most common malignancy in pregnancy [3]. Melanoma is a significant proportion of all tumors diagnosed during pregnancy, and this figure is up to 25% among all tumor diseases during gestation. There is continuing controversy concerning the

prognosis of women diagnosed with melanoma during pregnancy. Initial concerns about pregnancy's impact on prognosis in women diagnosed with melanoma date back to case reports from the 1950s. These reports suggested that pregnancy might lead to transformation of nevi into melanomas, increase the growth rate of existing melanomas, and cause localized melanomas to metastasize [4]. Subsequently, multiple observations seemed to support the argument that melanoma is a hormonally responsive malignancy: changes in skin pigmentation during pregnancy, detection of hormone receptors on some melanomas using older technology, a higher incidence of melanoma after puberty, and relative immunosuppression during pregnancy. The management of women diagnosed with melanoma during pregnancy is likewise controversial, particularly concerning sentinel lymph node biopsy (SLNB) and decisions about the management of the patient with nodal or metastatic disease [5]. Multiple studies have looked at the relationship between pregnancy and cutaneous melanoma. Factors limiting the interpretation of the literature include the following:

- Many of the case series prior to the 1980s did not account for the most important prognostic factors, such as depth of tumor or stage of disease. Subsequently, there have been a number of small case-control studies and large population-based cohort studies. While the case-control studies have the advantage of including important prognostic factors, the small numbers of patients included are an important limitation. Conversely, the larger cohort studies lack complete data on staging and Breslow depth.

- Some of the larger studies do not distinguish between diagnosis of melanoma during pregnancy and diagnosis during the postpartum period. Such studies refer to these patients as having pregnancy-associated melanoma (PAM). The definition of PAM varies in different studies and ranges from diagnosis during pregnancy to diagnosis up to 5 years after delivery [6].

- There is significant variability in the techniques and quality of the statistical analysis of the data between studies and in the presence of age-matched nonpregnant control groups, as well as a lack of consideration of important confounding factors, including but not limited to age, anatomic site of lesion, sun exposure or season at time of diagnosis, depth of the melanoma, the absence or presence of ulceration, and the presence as well as number of mitoses per mm^2 [2].

2. Definition

Deciding on the role of pregnancy in the development of melanoma is important, as more women are planning a pregnancy from 30 to 40 years, and an increase in the number of melanoma diagnoses during fetal growth is expected [3, 4]. Currently, the term "melanoma associated with pregnancy" is used, implying the inclusion of all clinical observations of the diagnosis of melanoma during pregnancy and in the first 2 years after delivery [5].

2.1 Diagnosis prior to pregnancy

Few studies have addressed the impact on prognosis when melanoma is diagnosed before a woman becomes pregnant, but based upon the available data, there does not appear to be an effect on prognosis. In a large Swedish retrospective cohort study [6], 966 women who had pregnancies after a diagnosis of a primary

melanoma were compared with 4567 women who did not become pregnant after diagnosis. After adjustment for Breslow depth, tumor site, Clark level, and age, pregnancy did not significantly affect survival (HR 0.58, 95% CI 0.32–1.05). For patients with a history of melanoma and multiple dysplastic nevi, we suggest more frequent dermatology examinations during pregnancy [7].

2.2 Diagnosis during pregnancy

Most of the multiple small controlled studies and large population-based cohort studies [6] do not show a negative influence of pregnancy on survival [2]. In a review of 10 case-control studies that included 185 women diagnosed with melanoma during pregnancy and 5348 women of the same childbearing age who were diagnosed with melanoma but were not pregnant, pregnancy did not have an impact on survival and did not increase the risk of a second melanoma [8]. The higher the parity and the younger the age of the mother at her first delivery, the lower the risk of melanoma. Thus, the authors concluded that there was no reason for physicians to recommend deferral of subsequent pregnancies in women who have been diagnosed with a stage I melanoma during a previous pregnancy [1]. A controversial study is a single-institution study that compared 41 women diagnosed with PAM with a control group of women of childbearing age who were not pregnant within 1 year of diagnosis [9]. PAM was defined as melanoma diagnosis either during pregnancy or within 1 year after delivery. After adjustment for stage, age, and location, the PAM group showed a five-, seven-, and ninefold increase in mortality, metastasis, and recurrence, respectively, when compared with controls.

2.3 Diagnosis postpartum

Multiple large population-based cohort studies [3, 10] and one small controlled study have generally found no influence on prognosis when melanoma is diagnosed up to 5 years following delivery, except for one study that observed an enhanced risk of death from melanoma in the first year postpartum, which may be due to delayed diagnosis during pregnancy. A large retrospective English study that linked data from a national cancer registry and hospital discharge data evaluated patients diagnosed with melanoma up to 5 years postpartum [10]. There was a significant increased death rate in the first year after delivery (HR 1.92, 95% CI 1.32–2.79) but not in the four subsequent years postpartum. Another study found a lower incidence of melanoma diagnosed during pregnancy than expected compared with the first 6 months postpartum [2]. The spike in melanoma diagnosis and death in the early postpartum period may be caused by a delay in diagnosis.

3. Classification

The eighth edition of the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system is based upon an evaluation of the primary tumor, the regional lymph nodes and lymphatic drainage, and the presence or absence of distant metastases. The information from TNM staging is then combined to classify patients into AJCC prognostic stage groups. There are four major growth patterns of melanoma: lentigo maligna, nodular, superficial spreading, and acral lentiginous. In an observational study of close to 120,000 patients with melanoma, nodular melanoma was an independent risk factor for death, after controlling for thickness, ulceration, and stage [11]. Nevertheless, the eighth edition of the American Joint Committee on Cancer tumor, node, and metastasis staging system,

which relies upon the primary tumor thickness and other features, involvement of regional lymph nodes, and presence or absence of distant metastases, should be used to stage melanomas of any growth pattern. Most melanomas arise as superficial tumors that are confined to the epidermis, where they may remain for several to many years. During this stage, known as the horizontal or "radial" growth phase, the melanoma is almost always curable by surgical excision alone. Melanomas that infiltrate into the dermis are considered to be in a "vertical" growth phase and have metastatic or "tumorigenic" potential. Nodular melanomas have no identifiable radial growth or in situ phase and appear to enter the vertical growth phase from their inception, resulting in thicker tumors at diagnosis.

In order to determine the stage of melanoma and, consequently, the physician's tactics and therapy regimen, it is common to use the levels of Clarke's invasion (1969), as well as the international TNM system. The level of invasion by Clark allows you to determine the number of layers of the epidermis affected by melanoma at the time of its detection. The system for determining the level of invasion according to Clark is historically the first system for determining the stage of invasion of melanoma into the epidermis, according to which tumors are divided into five stages (**Table 1**).

The depth of invasion is determined by the stages of Breslow (1970) [12]:

- Thin: the depth of invasion is less than 0.75 mm.

- Intermediate: the depth of invasion is 0.76–3.99 mm.

- Thick (deep): the depth of invasion is more than 4 mm.

After establishing the categories T, N, and M, they are grouped to determine the stage of the disease, which is expressed in Roman numerals from I to IV.

Stage 0: melanoma in situ (Clark level I), 99.9% survival rate
Stage I/II: invasive melanoma, survival rate of 89–95%
T1a: primary tumor thickness less than 1.0 mm, without ulceration $<1/mm^2$
T1b: primary tumor thickness less than 1.0 mm, with ulceration $\geq 1/mm^2$
T2a: thickness of the primary tumor 1.01–2.0 mm, without ulceration.
Stage II: high-risk melanoma, 45–79% survival
T2b: primary tumor thickness 1.01–2.0 mm, with ulceration
T3a: primary tumor thickness 2.01–4.0 mm, without ulceration
T3b: primary tumor thickness 2.01–4.0 mm, with ulceration
T4a: thickness of the primary tumor is more than 4.0 mm, without ulcerationT4b: thickness of the primary tumor is more than 4.0 mm, with ulceration.
Stage III: regional metastases, survival 24–70%
N1: single lymph node affected
N2: from two to three affected lymph nodes or regional metastases of the skin
N3: four affected lymph nodes or one lymph node with regional skin metastases.
Stage IV: distant metastases, survival rate of 7–19%
M1a: distant skin metastases, normal LDH.
M1b: lung metastases, normal LDH.
M1c: other distant metastases or any distant metastases with elevated LDH [6, 8].

The American Joint Committee on Cancer recently published its eighth edition of staging criteria, which went into effect as of 1 January, 2018. The impact of Breslow depth and mitoses has been adjusted in the new AJCC staging. The most significant change is that all tumors with a Breslow depth of 0.8–1.0 mm are now staged as T1b. Non-ulcerated tumors with a Breslow depth of <0.7 mm are still

Clark stage	Characteristics	Patient survival
The level of invasion I	All tumor cells are in the epidermis and do not reach the basal membrane	98–100%
The level of invasion II	Tumor cells infiltrate the papillary layer of the dermis	72–96%
The level of invasion III	The tumor reaches the border between the papillary and reticular dermis. The tumor enters the phase of vertical growth	46–90%
The level of invasion IV	Tumor cells are detected in the reticular layer of the dermis	31–67%
The level of invasion V	The tumor invades in the fatty tissue	12–48%

Table 1.
Microscopic melanomas by Clark (1969) [7].

classified as T1a. In addition, Breslow depth is now reported to the nearest 10th decimal place. Therefore, with rounding, T1b tumors encompass 0.75–1.04 mm or any ulcerated tumor of <0.7 mm [8]. Mitoses are no longer part of the criteria to upstage from T1a to T1b. There were no changes to T2–T4 staging. The clinical stage groups were not altered; T1a is still stage 1A, and T1b is still stage 1B [8].

4. Etiopathogenesis

One of the theories supporting the possible effect of pregnancy on tumor transformation is that pregnancy is considered a state of immunodeficiency, necessary to prevent the development of an immune response to fetal antigens. Although the exact mechanism by which tolerance to the fetus development is unclear, several immunological changes may allow the fetus to develop and grow. During pregnancy, the level of granulocytes increases, the number of monocytes remains unchanged, and a significant decrease in lymphocytes is also observed. T-lymphocyte activity is suppressed, and a disruption in the production of interleukins and interferon-G is demonstrated. However, the function of B-lymphocytes remains unchanged, and therefore the immune system during pregnancy is described as a bias toward the humoral immunity, which is more responsible for the formation of antibodies. This change in the balance of Th1 and Th2 cells is similar to the immunological state of patients with oncology [6]. Another possible mechanism of fetal tolerance involves the secretion of protein B7-H1 (CD274) by trophoblast cells; the B7-H1 protein induces apoptosis of activated T cells. This is important because it is also reported that melanoma can elude immune surveillance and secrete B7-H1. The combined secretion of B7-H1 can lead to the fact that melanoma during pregnancy grows and metastasizes more quickly. In addition, it was found that human leukocyte antigen HLA-G is expressed by placental trophoblast cells. Recent studies have shown the role of mutations BRAF V600E in 50% of all skin melanoma development [9]. The fact is that under the influence of excessive UV irradiation, there is a V600 mutation consisting of replacing valine with leucine (V600L), lysine (V600K), or glutamic acid (V600E) in the 600th position, which serves as a signal for the onset of neoplastic transformation. An important role in determining the prognosis is also the age and gender of the patient (women have a better prognosis), tumor localization, lymph node involvement, and the presence of tumor suppressor genes

(CDKN2A, CDK4) and proliferative markers (PCNA, Ki-67) and the presence of thromboses and thromboembolism. Thrombotic complications are the most common complications of paraneoplastic syndrome, manifested by arterial and venous thrombotic occlusions, migrating thrombophlebitis, pulmonary embolism, palpable non-bacterial thromboendocarditis, paradoxical bleeding, and thrombotic microangiopathy. Clinically, venous thromboembolism and malignant neoplasm have two main manifestations: firstly, thrombosis can be the only clinical manifestation of the tumor process, and secondly, in patients with cancer at all stages of the disease, thrombosis may develop [7, 10, 11]. Approximately 10% of melanomas are familial. Among subjects from melanoma families, defined as kindreds in which melanoma occurred in two or more blood relatives, the likelihood of developing melanoma is even greater among those family members who have dysplastic nevi. In a subset of these kindreds, the apparent familial pattern of inheritance may be attributable to clustering of sporadic cases in families who share common heavy sun exposure and susceptible skin type, making genetic analysis and risk stratification more challenging. This concept is substantiated by studies in which *CDKN2A* mutation status, sun exposure, and prevalence of dysplastic/benign nevi influence melanoma risk in families unselected for family history as well as melanoma-prone families.

5. Factors of the risk and clinical picture

The clinical recognition of melanoma, and in particular of early melanoma, may be challenging, even for the most experienced dermatologist. It has been estimated that the sensitivity of the clinical diagnosis of experienced dermatologists is approximately 70% [13]. However, the use of diagnostic aids such as dermoscopy, which requires some training, may greatly improve the sensitivity and specificity of the clinical diagnosis [14].

5.1 History and risk factors

Key questions that should be asked to patients presenting with a lesion that is of concern or for a general examination of their nevi include:

- When was the lesion (or a change in a preexisting lesion) first noticed?

- Does the patient have a personal or family history of melanoma or other skin cancers?

- Does the patient have a history of excessive sun exposure and/or tanning bed use?

- Did the patient suffer severe sunburns during childhood or teenage years?

- Does the patient have a cancer-prone syndrome (e.g., familial atypical multiple mole-melanoma syndrome or xeroderma pigmentosum)?

- Is the patient immunosuppressed?

- Did the patient receive prolonged psoralen plus ultraviolet A (PUVA) therapy?

The patient's phenotypic features associated with an increased risk of melanoma should also be assessed. They include:

- fair-complexioned phototype

- red or blond hair

- light eye color

- presence of a large number (>50) of melanocytic nevi (common nevi)

- presence of atypical melanocytic nevi (benign nevi that clinically share some of the clinical features of melanoma, such as large diameter, irregular borders, and multiple colors)

Clinicians assess the probability that a pigmented lesion is a melanoma using a complex cognitive process that includes a combination of the following steps: visual analysis and pattern recognition, comparative analysis of nevus patterns in an individual patient, and dynamic analysis:

- Visual analysis and pattern recognition typically assess whether a given pigmented lesion has one or more features that may suggest melanoma, including asymmetry, irregular borders, variegated color, and diameter > 6 mm. These features have been included in the widely adopted ABCDE checklist: **A**symmetry (if a lesion is bisected, one half is not identical to the other half), **B**order irregularities, **C**olor variegation (the presence of multiple shades of red, blue, black, gray, or white), **D**iameter ≥ 6 mm, and **E**volution (a lesion that is changing in size, shape, or color or a new lesion, a clinical prediction rule that was devised to help clinicians and laypeople identify suspicious lesions).

- The intrapatient comparative analysis uses the so-called "ugly duckling" sign, which refers to the presence of a single lesion that does not match the patient's nevus phenotype (the so-called signature nevus).

- A history of change in size, color, or shape of a preexisting melanocytic lesion (the "E" for "evolution" in the ABCDE checklist) is the most important clinical criterion for the diagnosis of melanoma. A change can be noted by the patient or documented by comparison of serial clinical or dermoscopic images.

6. Management of melanoma during pregnancy

The evaluation and management of the pregnant woman are similar to that of the nonpregnant woman and are based upon the stage of disease. However, there are potential concerns that arise even in the initial biopsy of suspected melanoma. As the stage of disease becomes more advanced, evaluation and management decisions become more complex in order to ensure safety of the mother and the fetus [1, 2].

A changing pigmented lesion during pregnancy that is clinically and dermatoscopically of concern as a possible melanoma should be biopsied immediately, as it would be in a nonpregnant patient. Excisional biopsy is the optimal way to evaluate a primary cutaneous melanoma. If the pregnant patient is considered a candidate for sentinel lymph node biopsy, there is controversy about the technique and timing of the procedure. In the case of a woman with advanced melanoma, imaging studies may be considered. According to a Committee Opinion Summary published by the American College of Obstetrics and Gynecologists' Committee on Obstetric

Practice, chest radiograph with appropriate shielding, ultrasonography, and magnetic resonance imaging (MRI; preferably without gadolinium) are the techniques of choice for imaging of the pregnant female [15]. In addition, studies such as other radiography, computed tomography (CT) scan (without contrast), and nuclear medicine imaging studies can be utilized since they are typically administered at doses that do not lead to fetal harm.

Some studies have suggested that melanomas diagnosed during pregnancy are more often of greater Breslow depth [16], but a larger proportion of studies have not observed a significant difference. Likewise, a retrospective review analyzed both clinical and pathologic characteristics of 34 melanomas diagnosed during pregnancy and up to 1 year after delivery and compared these with melanomas from age- and disease-matched controls. There was no significant difference in Breslow depth, ulceration, mitotic rate, stage of disease, anatomic location of the primary tumor, histologic subtype, Clark level, regression, necrosis, or vascular invasion [2].

While melanoma is the most common cancer to metastasize to the fetus, metastasis across the placenta to the fetus is rare and is only observed in women with widely metastatic disease [17–19] (**Figure 1**). Even if placental involvement with melanoma is identified, it has been estimated that the fetus is affected in only 25% of these cases. In cases of maternal advanced disease, it is important to alert the pathologist to perform meticulous sectioning of the placenta since many sections may be needed to detect small foci of melanoma.

The general approach to the treatment of pregnancy-associated melanoma is based upon the same prognostic factors as for nonpregnant woman. Melanoma diagnosed during pregnancy is a rare clinical case presentation which must be mastered. In the absence of guidelines for this clinical challenge, we performed a review of the literature and provide a practical guideline on how to manage such rare clinical cases based on our clinical experience. Expecting mothers require adequate counseling and explanation of all therapeutic options as they take responsibility for more than their own lives. However, they should be guided through the process of diagnostic and therapeutic measures in a potentially life-threatening situation. Pregnancy itself is no reason to withhold any type of necessary melanoma surgery. Perioperative management, however, requires certain adjustments in order to comply with this special situation. If indicated, even adjuvant and palliative systemic therapies need to be given to the patient, but they also have to be adapted to the specific circumstances as data is still sparse, especially for the new first- and second-line therapies with antibodies and targeted molecules.

Management becomes more complex once the need for SLNB is established or if the patient has more advanced disease and should be individualized. In advanced melanoma, the newest agents, such as BRAF inhibitors (vemurafenib and dabrafenib) and checkpoint inhibitors [nivolumab and ipilimumab (anti-programed cell death-1 and anti-CTLA, respectively)], may be teratogenic [17–21]. The FDA-approved patient labeling recommends avoidance of pregnancy and lactation during BRAF inhibitor therapy and up to 2 weeks after the last dose, during ipilimumab therapy and up to 3 months after the last dose, and during nivolumab therapy and up to 5 months after the last dose.

The patient with a thin melanoma with excellent prognosis need not delay future pregnancies or avoid the use of oral contraceptives or hormone replacement therapy, if the latter are indicated.

The combination of pregnancy and the high stage of melanoma are a dangerous condition requiring careful risk assessment by the obstetrician-gynecologist and oncologist. Earlier, women with melanoma III and IV stages were artificially interrupted by pregnancy according to medical indications. However, at present, in relation to risk stratification and pregnancy management in women with melanoma

associated with pregnancy, there is a view that therapeutic approaches are almost the same as those of nonpregnant ones and are determined by the stage of the disease. For patients with a history of melanoma and multiple dysplastic nevi, a more frequent dermatological examination during pregnancy is suggested. With regard to recommendations for the implementation of the reproductive function, it is shown that a future pregnancy should not be delayed in a woman with a thin localized melanoma with a favorable prognosis. For patients with progressive
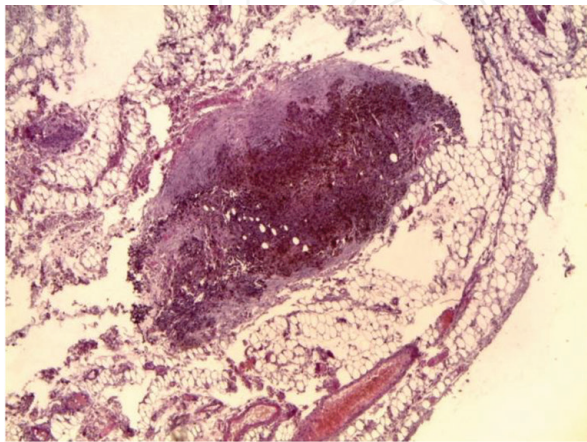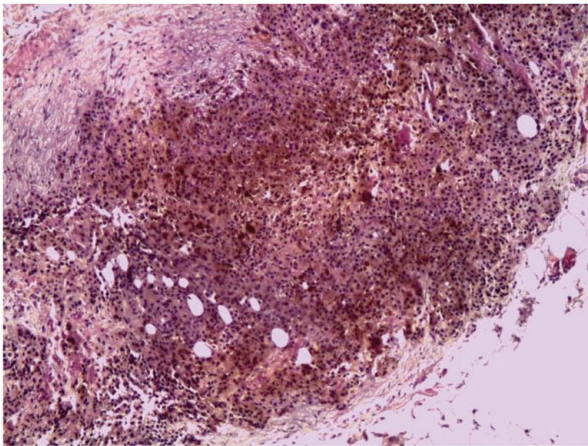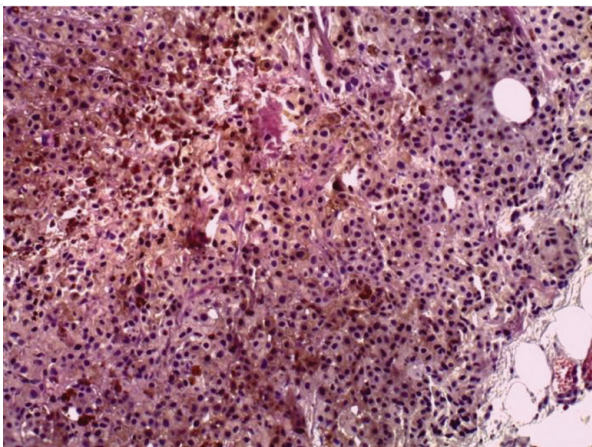
Figure 1.
Histological examination of biopsy (intraoperative) material (hematoxylin-eosin staining). The material is represented by a lymph node located among adipose tissue with tumor metastasis (a), which has the structure of epithelioid cell melanoma with a high content of pigment (b). The tumor totally replaces the tissue of the lymph node with the germination of the capsule (c).

disease, it is recommended to wait at least 2–3 years before pregnancy, since during this time interval relapses are most likely [13, 15, 22]. However, this issue should be considered individually in each specific observation, since a woman of late reproductive age may be concerned about the implementation of reproduction in the event of a pregnancy failure. The problem becomes even more controversial in a woman with a common form of the disease, because her life expectancy remains unclear. Decision-making becomes much more complex in the woman with a more uncertain prognosis where a delay in future pregnancy may be considered, but this should be evaluated on a case-by-case basis.

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