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Review

Prognosis for women diagnosed with melanoma during, before, or after pregnancy: Weighing the evidence

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ABSTRACT

Approximately one third of women who are diagnosed with malignant melanoma are of childbearing age. Therefore, it is not surprising that some studies have found malignant melanoma to be one of the most common malignancies diagnosed in pregnant women. The impact of pregnancy-related hormonal changes on melanoma development and progression remains controversial. Women undergo immunologic changes during pregnancy that may decrease tumor surveillance. Additionally, hormone receptors are found on some melanomas. Unfortunately, many of the past and even recent studies that have been published and are reviewed herein did not uniformly use appropriate control groups, account for confounding covariates, or employ appropriate statistical analysis, which makes it difficult to rely on the conclusions they reach. However, a review of the better controlled and preponderant studies demonstrates that pregnancy-associated melanomas are not associated with a poorer prognosis.

Introduction

Malignant melanoma (MM) is among the most common malignancies to affect young women (Bradford et al., 2010). Approximately one third of women who are diagnosed with MM are of childbearing age, and according to a recent Swedish population-based study, MM is the most common malignancy that is reported during pregnancy (Andersson et al., 2015; Lens and Bataille, 2008). As the age of the pregnant population shifts increasingly into the fourth decade of life, understanding the implications of pregnancy on malignancy has never been more important.

Since the 1950s, multiple published case reports and series have described pregnancy as the impetus for nevus transformation into MM and metastasis of existing MM (Byrd and McGanity, 1954; Pack and Scharnagel, 1951). Such reports incited controversy over the prognosis and management of women who are diagnosed with MM during pregnancy (Byrd and McGanity, 1954; Conybeare, 1964; Pack and Scharnagel, 1951; Pennington, 1983; Riberti et al., 1981). It has even been suggested that MM that is diagnosed during pregnancy has such an ominous prognosis that surgical sterilization might be appropriate (Byrd and McGanity, 1954). The value of these provocative early publications is limited because they were not controlled studies and did not account for important prognostic factors such as tumor depth. Yet, these clinical observations appeared reasonable because they aligned with emerging concepts on the immune system's role in tumor suppression and the immunomodulatory effects of pregnancy.

Pregnancy has long been known to induce a state of relative immunosuppression considered an adaptation to accommodate the growing fetus that contains foreign paternal antigens (Betz, 2012). This conventional wisdom has been validated at cellular and molecular levels, where the pregnant immune system abandons its usual T helper cell 1 dominance (in favor of an immune attack) to assume a more tolerant T helper cell 2 dominant phenotype (Nevala et al., 2009; Wei et al., 2010). This permissive immune environment is characterized by the upregulation of immunosuppressive T-regulatory cells and uterine natural killer cells, which are immunomodulatory cells that are similar to those that are upregulated by some tumors to induce tumor tolerance (Holtan et al., 2009; Leber et al., 2010).

Additional evidence has suggested that pregnancy-related hormonal changes have a direct effect on MM. The argument that MM has a hormonally responsive component is supported by reports that demonstrate changes in pigmentation during pregnancy, increased MM incidence after puberty, and the presence of progesterone and estrogen receptors in some MM patients (de Giorgi et al., 2009; Grill et al., 1982; Gupta and Driscoll, 2010; Mitov et al., 2015; Moller et al., 2013; Neifield and Lippman, 1980; Schmidt et al., 2006; Zhou et al., 2014).

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While early case reports and series supported the apparent link between pregnancy and a poorer prognosis, many recent studies have observed no significant effects on survival in women who are diagnosed with localized MM (American Joint Committee on Cancer stage I or II) before, during, and after pregnancy (Daryanani et al., 2003; MacKie et al., 1991; McManamny et al., 1989; Reintgen et al., 1985; Slingluff et al., 1990; Wong et al., 1989). These latter studies used appropriate control groups and considered stage of disease and important prognostic factors such as tumor thickness and location. Even those rare reports of stage III and IV melanoma in pregnant women who undergo therapy did not show a difference in survival when compared with nonpregnant patients (Pagès et al., 2010). However, some of the more recent large cohort studies do not separate MM that is diagnosed during pregnancy from MM that is diagnosed during what the authors view as the pre- and post-partum period. Investigators refer to these cases as pregnancy-associated MM (PAMM), and the timing of diagnosis varies from a year prior to pregnancy, during pregnancy, and as much as 5 years postpartum (Johansson et al., 2014). Although the population-based cohort studies offer the advantage of large numbers of patients, data are often incomplete with regard to Breslow depth of the primary tumor and stage of disease. Some studies do not report the duration of follow-up or adjust for possible confounding factors such as location of the primary tumor. A few recent studies have fueled the controversy by suggesting a poorer prognosis for PAMM (Byrom et al., 2015; Tellez et al., 2016).

Herein, we present evidence on both sides of the controversy. We first address studies that indicate that PAMM has an adverse influence on prognosis, followed by studies that observed no impact of pregnancy on prognosis. Our analysis will examine data from women who are diagnosed with MM prior to pregnancy, during pregnancy, and in the postpartum period, and consider only those studies that included Breslow depth, appropriate control groups, and stage of disease.

Melanoma diagnosed during pregnancy

Evidence: Pregnancy is associated with a poorer prognosis

Two studies that used data from the same institutional database showed a shorter disease-free interval (DFI) in the group of pregnant patients compared to control subjects. Using patient information from a single institution, Reintgen et al. (1985) studied 58 patients who were diagnosed with localized MM during pregnancy. A later study by Slingluff et al. (1990) added additional patients to the pregnant cohort for a total of 88 patients. For both studies, while actuarial survival curves showed no significant difference in survival between the groups, actuarial DFI curves showed that women who were diagnosed with MM during pregnancy had significantly shorter DFIs ($p = .039$ [Slingluff et al., 1990] and $p = .04$ [Reintgen et al., 1985]). Multivariate regression analysis in both studies, including important prognostic factors such as tumor thickness and ulceration, showed that pregnancy was significant in its effect on shortening DFI. Reintgen and colleagues speculated that the duration of follow-up (mean, 5 years) might have been too brief to observe an effect of pregnancy on survival, and because the group of pregnant patients was followed for a longer period of time, there may be an influence on survival. An alternative hypothesis offered was that pregnancy may shorten DFI without having an influence on survival (Reintgen et al., 1985). It is worth noting that the only variable found to impact survival was tumor thickness.

Several additional studies reported marginally-to-significantly elevated hazard ratios (HRs) for PAMM-related deaths. Using data from the Cancer Registry and the Medical Birth Registry of Norway, Stensheim et al. (2009) reported an increased risk of MM-related death in 160 pregnant patients compared with 4460 nonpregnant patients (HR 1.52, 95% confidence interval [CI] 1.01-2.31). However, once the melanomas were adjusted for anatomic location, there was no statistically significant difference in survival (HR 1.45, 95% CI 0.96-2.21).

A recent meta-analysis reported an increased risk for MM-related death (pooled HR 1.56, 95% CI 1.23-1.99; Byrom et al., 2015). However, the methodology of this study has been contested by several investigators (Kyrgidis et al., 2016; Matires et al., 2016b). The meta-analysis is limited to studies that utilize multivariable methods that report HR with CI and excludes a large study by O'Meara et al. (2005), which reported an HR for PAMM mortality of 0.79 ($p = .57$).

Such a model with so few studies appears insufficient to compensate for the heterogeneity among the studies with regard to definitions of PAMM and study design. In our own meta-analysis of studies that evaluate the prognosis for PAMM, we found a nonsignificantly elevated risk of death for pregnant patients who were diagnosed with melanoma (HR 1.19, 95% CI 0.96-1.48; Matires et al., 2016b). This markedly different result is obtained simply by including additional studies that were omitted by Byrom et al. (2015) in their study.

A single institutional retrospective study that was conducted by Tellez et al. (2016) recently reported a mortality rate of 20% and a 5-fold greater odds of death ($p = .03$) in patients with PAMM (diagnosed during pregnancy or within 1 year postpartum) than in nonpregnant women. The mortality rate and odds ratio that were reported are substantially higher than those in all prior studies in the literature. This study appears to offer a convincing argument as it addresses much of the bias that plagued earlier studies of its type. Information with regard to staging was available in all cases and the analysis accounted for Breslow depth, tumor location, and age.

However, this study shares several shortcomings with its predecessors and conclusions should therefore be interpreted with caution. The number of patients with more advanced disease differs between the published text and associated Table 2 without any description of upstaging. This disparity has a significant effect in an analysis that includes only small numbers of patients with PAMM. Investigators used logistic regression rather than survival and progression-free analysis (Matires et al., 2016a). Finally, this study included only 41 PAMM cases, of which a mere 19 were diagnosed during pregnancy (Tellez et al., 2016). Similar earlier survival studies by Lens and Bataille (2008), O'Meara et al. (2005), and Johansson et al. (2014) examined cohorts with pregnant patients in the hundreds (185, 145, and 247 respectively).

This single tertiary care center study is the source of renewed controversy on the subject of PAMM. Although the results are evocative enough to warrant additional larger, well-crafted, population-based studies of this type, the outcomes of these 19 patients are not sufficient to direct the treatment or counseling of women who are diagnosed with MM during pregnancy.

Evidence: Pregnancy has no influence on prognosis

In contrast to the findings by Reintgen et al. (1985) and Slingluff et al. (1990), which are both studies that showed no difference in survival but suggested a difference in DFI for PAMM, three additional trials using patient data from separate databases found no significant effect of pregnancy on DFI.

A British study by McManamny et al. (1989) retrospectively evaluated 23 patients who were diagnosed with localized MM during pregnancy and compared them with 243 women who were neither pregnant before nor at the time of the diagnosis of MM. There was no significance in survival or DFI between the cohorts of pregnant patients and control subjects. Even though multivariate regression analysis was not performed, there was no significant difference between the two groups in tumor thickness or anatomic location of MM.

In another retrospective study by Wong et al. (1989), the prognosis for 66 patients who were diagnosed with localized MM during pregnancy was analyzed. There were no significant differences in the 5-year survival rate among the group of pregnant patients (86%), control subjects (87%), and the matched controls (92%). In fact, as opposed to the findings by Reintgen et al. (1985), mean DFI was actually longer in the pregnant patients compared with the matched controls (37.7 vs. 27.3 months, respectively). Furthermore, 41% of the pregnant patients in this study had tumors in poorer prognostic sites compared with 15% in the matched controls.

A study by MacKie et al. (1991) divided data from 388 women into four groups: women who were diagnosed with MM prior to pregnancy, during pregnancy, after all pregnancies, and those diagnosed between pregnancies. The patients who were diagnosed during pregnancy had MM in anatomic sites that portend a poorer prognosis and also exhibited significantly thicker tumors compared with control subjects. Once these factors were considered with multivariate regression analysis, the group of patients who were diagnosed during pregnancy did not differ significantly from the control subjects with respect to both survival and DFI. Pregnancy at the time of diagnosis was not a significant independent variable.

In contrast to the findings of Byrom et al. (2015) and Tellez et al. (2016), most recent studies reported no significant increase in mortality for pregnant women who were diagnosed with MM. In a retrospective cohort study using data from the Swedish National and Regional Registries, Lens et al. (2004) compared data from 185 women who were diagnosed with MM during pregnancy with data from 5348 age-matched, nonpregnant women who were diagnosed with MM. There was no statistically significant difference in overall survival between these groups (χ^2_1 [r] = .84, $p = .361$). The influence of pregnancy status was assessed with a multivariable Cox regression model for 2101 women with available data on Breslow depth of primary MM, Clark's level, anatomic site of MM, and age. Pregnancy status at the time of MM diagnosis was not related to death (HR 1.08, 95% CI 0.60-1.93). In a subsequent analysis, the investigators also calculated the risk of cause-specific survival and found no significant differences when comparing women who were diagnosed with MM during pregnancy with control subjects as assessed by log rank test ($\chi^2_1 = 0.11$, $p = .738$) or multivariable analysis (HR 1.17, 95% CI 0.59-2.32, $p = .658$; Lens et al., 2009).

O'Meara et al. (2005) used a database that associated California hospital discharge records with the California Cancer Registry to compare data from 412 women who were diagnosed with MM during pregnancy and up to 1 year postpartum with data from 2451 age-matched nonpregnant women who were diagnosed with MM. Kaplan-Meier survival curves showed no significant differences between the groups (log-rank test, $p = .13$). A Cox proportional hazards model assessed the impact of various factors on the risk of MM-related death including pregnancy status, Breslow depth of primary MM, stage of disease, and age. When the analysis was limited to data from the 145 women who were diagnosed during pregnancy, pregnancy status was not related to death (HR 0.79, $p = .570$). The mortality rate was reported as 8.3% in the group of pregnant patients compared with 9.8% in the control group.

A population-based retrospective cohort study based on data from the Swedish Cancer and Multi-Generation Registers compared cause-specific mortality in data from 1019 women with MM that was diagnosed during pregnancy or up to 2 years postpartum with data from 5838 women who were not pregnant or within 2 years postpartum at the time of diagnosis (Johansson et al., 2014). When the PAMM group was limited to data from the 247 women with MM that was diagnosed during pregnancy and compared with data from the control subjects, there was no significant difference in mortality (HR 0.79, 95% CI 0.44-1.41) with HR adjusted for time since diagnosis, age at diagnosis, calendar year at diagnosis, education, parity, and tumor location.

The results of some of these studies should be interpreted with caution. The small studies were frequently limited to early-stage disease (American Joint Committee on Cancer Stage I or II). In contrast, the large population-based cohort studies included all stages of disease, and information with regard to stage varied widely. O'Meara et al. (2005) reported stage of disease for 108 of 145 pregnant patients (74.5%), and 92.6% of these patients had localized MM. The study by Johansson et al. (2014) was missing stage information in 39.4% of cases. Stage of disease was not reported in the Swedish study by Lens et al. (2004).

In summary, on the basis of a small number of appropriately controlled studies, women who are diagnosed with MM during pregnancy do not appear to have a poorer prognosis than nonpregnant control subjects. Of note, some studies have even demonstrated that women with a history of higher parity (especially five or more live births) and earlier age at first birth were at a significantly lower melanoma risk than nulliparous women (Lens and Bataille, 2008).

Melanoma diagnosed in the postpartum period

Evidence: Diagnosis in the early postpartum period negatively influences prognosis

One study that examined PAMM, breast cancer, and Hodgkin's lymphoma reported significantly increased mortality in patients who were diagnosed with MM in the first year postpartum. An English cancer registry study that examined the prognosis for several malignancies in the postpartum period reported significantly increased mortality in patients who were diagnosed with MM in the first year postpartum (HR 2.06, 95% CI 1.42-3.01) compared with women in the control group but not for those diagnosed in the second through fifth year postpartum (Moller et al., 2013). This observation may be related to a delayed diagnosis because MM is disproportionately diagnosed in the initial postpartum period after being overlooked and allowed to progress during pregnancy. In support of this theory, others have reported fewer than expected melanomas that are diagnosed during pregnancy and a higher rate that are diagnosed 6 months postpartum, which possibly represents a rebound effect that is caused by a delay in diagnosis (Andersson et al., 2015).

Evidence: Diagnosis in the early postpartum period has no influence on prognosis

In the most recent and largest study from the Swedish Cancer and Multi-Generation Registers, there was no evidence of a worse prognosis for patients diagnosed with MM during pregnancy and up to 2 years postpartum except for a difference in the second year postpartum that was not statistically significant (Johansson et al., 2014). The analysis was extended through 5 years postpartum, and no differences in survival by year were found.

In summary, five controlled studies have examined the impact on prognosis when MM is diagnosed after pregnancy with inclusion of up to 5 years postpartum. One study showed a negative influence in the first year after delivery, but overall, the evidence to date does not suggest a worse prognosis for women who are diagnosed with MM up to 5 years postpartum.

Melanoma diagnosed prior to pregnancy

Evidence: Diagnosis prior to pregnancy has no influence on prognosis

On the basis of very few studies, there is no significant impact on prognosis when MM is diagnosed prior to pregnancy. Overall, there is

a paucity of studies that address the influence of MM on prognosis when diagnosed before pregnancy. In the retrospective, population-based cohort study by Lens et al. (2004), a secondary analysis compared data from 966 women with MM that was diagnosed prior to pregnancy to data from 4567 women without pregnancy after an MM diagnosis. Using a multivariable Cox regression model, MM that was diagnosed prior to pregnancy was not related to survival after adjustment for Breslow depth of tumor, tumor site, Clark's level, and age (HR 0.58, 95% CI 0.32-1.05). Reintgen et al. (1985) found no difference in survival between data from 43 women who became pregnant within 5 years of their MM diagnosis and 337 non-pregnant, age-matched control subjects in both univariate and multivariable models. Similarly, MacKie et al. (1991) compared data from 85 women who became pregnant after a diagnosis of MM with data from 143 patients who completed all their pregnancies prior to the MM diagnosis and found no significant difference in overall survival or DFI. In summary, there appears to be no influence on survival when MM is diagnosed prior to pregnancy.

Conclusion

On the basis of a limited number of studies, pregnancy appears to have no influence on the prognosis of MM that is diagnosed prior to pregnancy, during pregnancy, or after pregnancy. At this time, there is no evidence to warrant postponing or terminating pregnancies in women who are diagnosed with early-stage disease. This conclusion is based on the best available data from the relatively few studies that have employed control groups, appropriate cohort sizes, and statistical analysis to control for confounding variables. Unfortunately, because few studies from the past half-century meet these criteria, there is still uncertainty with regard to prognosis and recommendations for expectant mothers. For now, the primary consideration for a pregnant woman's prognosis continues to be identical to that for the nonpregnant woman. Prognosis is based on the stage of disease, tumor thickness, presence or absence of ulceration and mitoses, and the spread of MM to the lymph nodes and other organs. The studies we discussed highlight both the power and pitfalls of metadata analysis. It is important that future research includes larger cohorts of pregnant patients and control for the most important variables such as tumor depth, location, and stage of disease. As tumor registries and other such databases accumulate larger patient numbers with more complete patient and tumor data, metadata analyses promise more compelling evidence concerning the prognosis of PAMM.

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