Pregnancy and Melanoma: What We Know About the Risks

Against a backdrop of conflicting findings, a new study suggests a significant risk associated with melanoma during pregnancy.

BY JONATHAN WOLFE, MD

Pregnancy associated melanoma (PAM or pregnancy associated malignant melanoma: PAMM)—melanoma that appears during pregnancy or within one year after delivery—has been an area of research interest for some time. Findings have been inconsistent with regard to the influence of pregnancy on risk for developing melanoma or on melanoma outcomes. A recent publication suggests, however, that women who develop melanoma during pregnancy may be at increased risk for mortality. Ahead is a review of some of the research to date and a closer look at the latest findings.

BACKGROUND: STUDIES TO DATE

When researchers analyzed five databases (Cochrane Database, MEDLINE, EMBASE, CINAHL, and PubMed) to explore the effect of subsequent pregnancy on risk of melanoma death or recurrence, they found no evidence for a negative effect of pregnancy. However, Byrom et al. noted that the evidence is sparse.1

The authors collated all longitudinal studies of women of childbearing age diagnosed with incident melanoma that compared melanoma outcomes among those who became pregnant after the diagnosis and those who did not. Individual study effect estimates were pooled when available using the weighted average method, and other findings were summarized narratively. Of the five studies included in the analysis, all assessed melanoma death, and two assessed recurrence. The authors found no significant effect of subsequent pregnancy on melanoma mortality after 11 to 20 years of follow-up and no significant differences in melanoma recurrence.1

This study garnered several responses,2,3 questioning the methodology and study conclusions. One letter to the editor challenged the inclusion and exclusion criteria for the Byrom study.3 Had the researchers included a 2014 study by Johansen, et al. (See below) and MacKie, et al. (Lancet, 1991) in their analysis, they would have found a not-statistically significant increase in PAM mortality, the letter authors argue.

Byron, et al. replied to the Martires letter by pointing out that Johansen, et al. included as PAM melanomas diagnosed up to two years post-partum, which is outside the standard definition of PAM. “Based on our findings and due to the limitations as stated in our manuscript, a precautionary attitude should prevail when managing patients with a pregnancy-associated melanoma,” they conclude.4

Johansen, et al.’s disputed population-based cohort study used the Swedish Cancer and Multi-Generation Registers. They estimated hazard ratios with 95% confidence intervals adjusted for age, period, education, parity, and tumor location. Researchers identified 6,857 women and girls aged 15 to 44 years with a diagnosis of cutaneous MM between 1963 and 2009. Of these, 1,019 cases were classified as PAM. Cause-specific mortality did not differ between PAM and MM not diagnosed near childbirth (adjusted hazard ratio 1.09, 95% confidence interval 0.83-1.42).5 The authors note that information on stage at diagnosis was not available for all patients, thus limiting analysis.

THE LATEST FINDINGS

For a study published this summer, researchers conducted a systematic review and meta-analysis to assess the effect on melanoma outcome of a coinciding pregnancy. The study was a systematic review and meta-analysis of risk of death from, or recurrence of, pregnancy-associated melanomas compared with other melanomas in women of reproductive age. Using the same five databases as Byrom, et al., the
researchers identified studies that investigated melanoma outcomes in women with PAM, included a comparison group, and reported measures of risk of melanoma death or disease-free survival. Individual study effect estimates were pooled using the weighted average method. Studies that did not report a quantitative estimate were summarized narratively. Assessed outcomes in the 14 studies that met the inclusion criteria were melanoma death (seven), recurrence (three), or both (four). Pooled estimates of mortality risk from four studies showed increased risk of melanoma death after adjustment for patient age and stage of melanoma for PAM compared with other melanomas. Based on limited quantitative evidence, the study concluded, pregnancy-associated melanomas appear to have poorer outcomes than other melanomas.

A retrospective cohort study reviewed medical records and pathology reports from women given a diagnosis of melanoma between 2006 and 2015. Tumor proliferation rates were analyzed using mitotic count and immunohistochemical markers of proliferation (phosphohistone H3 and Ki-67). The review included 50 PAM and 122 non-PAM cases, a diagnosis of melanoma in situ was associated with PAM. Among invasive melanomas, there was no difference in proliferative activity between groups. Pregnancy status was also not associated with age at diagnosis, tumor site, Breslow depth, Clark level, ulceration, or overall stage. The authors concluded that a history of PAM should not outweigh traditional factors (such as advanced maternal age) in planning future pregnancies in women given a diagnosis of stage I melanoma and are undergoing close surveillance.

The latest piece of information for consideration comes from an analysis of risk factors and outcomes of melanoma in women under age 50. The study did not investigate PAM solely, though it did find that patients with PAMM had 5.1 increased odds of death from melanoma compared with control subjects independent of stage, age, and melanoma location. Patients with PAMM had 6.7 increased odds of developing distant melanoma metastasis independent of stage, age, and location. The analysis included 41 patients with PAMM, 19 of whom were diagnosed while pregnant.

IMPLICATIONS

It has been hypothesized that pregnancy may mediate outcomes in cutaneous melanoma either through hormonal influences or relative immunosuppression. One retrospective study analysed the pathological characteristics and survival rate of PAM, compared to a cohort of non-pregnant age- and stage-matched control patients. Between 2003 and 2014, 34 pregnant women (aged 32.5 ± 5.6 years) were diagnosed with melanoma and included in the analysis. Pathological features, such as histologic subtype, Breslow thickness and Clark level, tumor cell type, mitotic rate, peritumoral inflammation, as well as ulceration, regression, necrosis, vascular invasion and presence of satellite were analyzed and related to clinical data. Researchers found that peritumoral inflammation and mild inflammation was higher in the PAM group. However, there were no differences in any other parameters between pregnant and non-pregnant melanoma cases.

While it remains to be seen whether pregnancy increases an individual’s risk for developing melanoma, there is now sufficient evidence to suggest that women who develop melanoma while pregnant may indeed have a poorer prognosis. It is important that dermatologists be attentive to the concerns of pregnant women who may seek evaluation of new, changing, or otherwise suspicious lesions, providing accurate diagnosis, appropriate treatment as needed, and long-term surveillance. Furthermore, outreach to those who provide care to pregnant women, most notably OB/Gyns,
should focus on education about the need to identify early and actively follow any melanoma that may develop in a pregnant woman. Identification of disease at its earliest stage remains the most effective way to manage melanoma.

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