Pregnancy and Estrogen Receptor β Expression in a Large Congenital Nevus

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Background: Large congenital nevi carry a slightly increased risk of melanoma. Pregnancy poses an additional challenge in the monitoring of these patients because little is known regarding the effects of increased estrogen levels on congenital nevi.

Observations: A young woman was observed to have clinical lightening of her garment nevus and satellite nevi during 2 sequential pregnancies. Postpartum, the patient experienced darkening and repigmentation in her large garment nevus, with continued lightening of nearby satellite lesions. In addition to photographic documentation of these changes, biopsy samples taken during pregnant and nonpregnant periods underwent immunohistochemical evaluation for estrogen receptor β (ERβ), the predominant estrogen receptor in nevi and melanomas. Biopsy samples collected during pregnancy showed a decrease in nuclear staining for ERβ compared with samples collected after pregnancy. These changes in ERβ expression were not associated with histologic atypia during pregnancy or after delivery.

Conclusions: Congenital nevi may be unique in their response to altered estrogen levels. Given the slightly increased risk of melanoma in giant congenital nevi and the dearth of information available regarding the effects of pregnancy on congenital nevi, this case illustrates the need for further study of these pigmented lesions.
evaluated the nevi of the patient for ERβ while she was pregnant and after pregnancy because ERβ is the predominant ER found in nevi and malignant melanomas. This evaluation revealed a decrease in expression of ERβ with pregnancy compared with that observed after parturition. The ERβ levels from the nevi of this patient have been averaged in a larger congenital nevi data set; however, the clinical course, with photography and detailed immunohistochemical findings, has not been previously presented, to our knowledge.

Figure. Clinical photographs and immunohistochemical stains from the study patient. Mild variation is seen in exposure secondary to different cameras used in the first photograph vs the remaining photographs. A, Photograph of the lower extremities of the patient, which show the large garment nevus on the right thigh (arrow) and smaller satellite lesions taken at the age of 6 years. B, Photograph of the lower extremities of the patient at the age of 23 years during her second pregnancy demonstrating part of the large congenital nevus on the right thigh and leg (arrow) and smaller satellite nevi that had lightened during the pregnancy. The arrowhead depicts the biopsy site for the immunostaining in parts D and E. The circled areas depict the biopsy sites. C, Photograph of the lower extremities of the patient 1 year post partum, which demonstrate darkening and repigmentation of the large garment nevus on the right leg (arrow) and a portion of the satellite lesion on the left thigh. The arrowhead depicts the site of focal darkening in the garment nevus and the biopsy site for the immunostaining in parts F and G. The circled areas depict the biopsy sites. D, Immunohistochemical analysis for estrogen receptor β (ERβ) of the changing large congenital nevus taken from the lower part of the right leg of the patient while 28 weeks pregnant (arrowhead in part B). The congenital nevus of the patient had exhibited clinical lightening throughout the pregnancy. This representative field shows a mixture of immunopositive (red) and immunonegative (blue) nevocytes for ERβ. Scale bar=660 μm. E (inset), Higher magnification of the lesion in part D that shows numerous ERβ-immunonegative nevocytes counterstained with hematoxylin (blue). Scale bar=164 μm. F, Immunohistochemical analysis for ERβ in the darkening large congenital nevus taken from the right thigh of the patient 1 year after parturition (arrowhead in part C). Note the intense immunoreactivity for ERβ, particularly in the more rounded, clustered nevocytes. There is also significant cytoplasmic staining. Scale bar=660 μm. G (inset), Higher magnification of the same lesion as in part F. Virtually every nevocyte exhibits immunopositive staining for ERβ (red), with rare exceptions. Scale bar=164 μm.

A 23-year-old white woman with a large bathing trunk nevus and multiple satellite nevi that covered nearly her entire cutaneous surface had been observed in the Vanderbilt University Pigmented Lesion Clinic for 18 years, beginning at age 5 years. Clinically, the pigmentation levels in her congenital nevus had remained stable throughout the years, including during her entrance into puberty. The
pigmentation levels changed when the patient became pregnant with her first child. Clinical examination of the patient at the time revealed diffuse lightening of her large garment nevus. Similarly, a “halo” effect and lightening without inflammation was noted in several of the smaller satellite nevi, particularly on the lower extremities. The patient delivered a healthy boy in the summer of 2004 and was not seen in the Pigmented Lesion Clinic until a year later, this time pregnant with her second child. Clinical evaluation documented decreased pigmentation of the large garment nevus and many of the satellite nevi. Biopsy samples (4-mm punch) were collected when the patient was at week 28 of gestation. These samples were collected from the lower part of her right leg (in the large garment nevus), the lateral part of her left leg, and the medial part of her left leg (lesions 5, 6, and 7, respectively, in the Figure, B). Immunohistochemical staining for ERβ was performed, and the intensity and percentage of the nuclear and cytoplasmic staining were recorded in an identical manner as in previous work by our group. Results for all the nevi samples studied are given in the Table. Epidermally located nevocytes were not found in these 3 biopsy samples; however, average ERβ nuclear staining for dermal nevocytes was 1.67 of a total score of 5. An example of the ERβ immunohistochemical results is shown in the Figure, D and E.

One year after the birth of her second child, the patient visited the clinic, concerned that “my moles have changed a little.” The patient was breastfeeding her infant daughter at this time. Clinical examination revealed 3 focal areas of darkening in the large garment nevus of the patient on the lateral part of her right thigh (lesion 5 in the Figure, C), right inguinal crease (lesion 6, not shown), and medial part of her right thigh (lesion 7 in the Figure, C). There was also continued lightening in several satellite nevi, particularly on the lower parts of her legs. Biopsy samples from these 3 lesions, along with a fourth sample (2 cm medial to lesion 5 in the Figure, C) of a nearby stable satellite nevus for comparative purposes, are shown in circles in the Figure, C. None of the nevi biopsied showed cytologic atypia, whether during pregnancy or postpartum. Immunohistochemical staining for ERβ revealed increased nuclear staining compared with the biopsy samples taken while pregnant, with dermal nuclear staining averaging 2.67 of a total staining score of 5. In addition, cytoplasmic staining, which was not observed in the biopsy samples during pregnancy, was seen in these samples, which averaged a staining score of 0.67 of 5 (Figure, F and G). At recent follow-up visits, while neither pregnant (20 months post partum) nor breastfeeding, the patient had continued to notice areas of darkening in her garment nevus and satellite nevi on the arms, although some of the satellite nevi on the legs remain less pigmented.

A review of the literature yields only 3 case reports that detail the effects of pregnancy on congenital nevi. Two of the cases were not typical for congenital nevi. One case involved a black patient with a congenital blue nevus that enlarged during pregnancy and was found in the postpartum period to have developed into a malignant melanoma. A congenital blue nevus is a rare entity and is not comparable with the present case. A separate case study from Italy noted no change in the congenital garment nevus of a patient while she was pregnant or in the postpartum period, in contrast to the present patient. The final case study reported the development of an agminated Spitz nevus in a congenital nevus during pregnancy. This nevus was also atypical for a congenital melanocytic nevus. This fourth case has the distinct finding of clinical lightening of a giant congenital nevus and satellite nevi during 2 pregnancies, with some repigmentation after parturition. This phenomenon was confirmed by photographic analysis of the congenital nevi of the patient before, during, and after pregnancy. To our knowledge, this occurrence has not been previously reported in the literature.

The present case report is also novel in that we evaluated the ERβ status in the lesions. Immunohistochemical staining for ERβ showed decreased staining in the congenital nevi during pregnancy and increased staining for ERβ after delivery, which suggests that congenital nevi may be less estrogen responsive during pregnancy. Previous work by our group found increased expression of ERβ in benign nevi removed from pregnant women and in atypical nevi from women regardless of pregnancy status. These previously published data, which included the ER staining data from this patient and 1 other patient who was pregnant and had congenital nevi, showed decreased staining for ERβ in congenital nevi from pregnant women compared with nonpregnant controls (n = 17). Based on the small number of patients with congenital nevi in these studies, it remains unclear whether this result typifies the normal effects of increased estrogen states on congenital nevi. Another limitation of this study is that biopsy samples were not collected from the same sites during and after pregnancy in this patient.

Along with clinical observation, the presence of estrogen receptors on melanocytes in nevi and melanoma suggests that these nevocytes are estrogen responsive. Historically, cases in the literature have reported an increase in size, thickening, or darkening of nevi during pregnancy, although recent evidence suggests that this may not be the case. We observed the unusual finding of clinical lightening along with decreased expression of ERβ during pregnancy in a patient with a

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<th>Location</th>
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<tr>
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<tr>
<td>Lesion 7 in the Figure, C</td>
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Table. Estrogen Receptor β Intensity by Location and Status

a Grading scale for assessment of level of estrogen receptor β staining: 0, less than 5%; 1, 5% to 25%; 2, 26% to 50%; 3, 51% to 75%; and 4, 76% and greater immunopositive cells.
giant congenital nevus and satellite congenital nevi. This suggests that decreased expression of ERβ in congenital nevi during pregnancy may lead to decreased production of melanin. Previous studies in melanocyte cell cultures suggest that estradiol increases tyrosinase and tyrosinase-related proteins 1 and 2 messenger RNA and upregulates the expression of melanocortin 1 receptor messenger RNA, presumably through ERβ. Therefore, a decrease in ERβ concentration might be expected to have the opposite effect and could possibly decrease pigmentation through these mechanisms (although estrogen levels would be expected to be high in pregnancy). Certainly, the apparently altered response of congenital nevi, particularly large garment nevi, during pregnancy compared with acquired nevi, bears further study. A better understanding of congenital nevi and their response to estrogen is also indicated because patients with large garment nevi have an increased risk of melanoma, and these patients can be difficult to observe and evaluate.1,4 We did not see any evidence of atypia in any of the congenital nevi we biopsied in this patient. This was an important observation because we previously noted decreasing levels of ERβ with increasing depths of melanomas.7 However, in light of the lack of histologic atypia, we do not believe that a similar mechanism is responsible for the decrease in ERβ concentration seen in congenital nevi with pregnancy. Although there are no conclusive data suggesting that pregnancy has a detrimental effect on the incidence or progression of melanoma,6,8 careful attention should still be given to the pregnant patient with pigmented lesions. Larger studies of pregnancy effects on patients with large congenital nevi are indicated because this review confirms that few data exist. Photograph documentation and dermoscopy may be useful in these patients for assessment and comparison purposes. Currently, the most effective method for evaluating and treating these patients remains close follow-up at regular and frequent intervals by a dermatologist trained in the evaluation of pigmented lesions.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Nannen and Ellis. Acquisition of data: Nading, Nannen, and Ellis. Analysis and interpretation of data: Nading, Nannen, and Ellis. Drafting of the manuscript: Nading, Nannen, and Ellis. Critical revision of the manuscript for important intellectual content: Nading, Nannen, and Ellis. Obtained funding: Ellis. Administrative, technical, and material support: Nading, Nannen, and Ellis. Study supervision: Nannen and Ellis.

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REFERENCES