

Melanoma and Pregnancy: 'Prompt Biopsy Is Key'

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SAN DIEGO — Pregnant women who present with changing nevi should not be treated differently from other patients of similar age, Dina R. Massry, M.D., said at a melanoma update sponsored by the Scripps Clinic.

"Prompt biopsy is key," said Dr. Massry, a dermatologist with the division of dermatology and cutaneous surgery at the Scripps Clinic-Torrey Pines, La Jolla, Calif.

While it is commonly accepted that nevi enlarge and change during pregnancy and that new nevi develop, pregnant women "may get a false sense of security and disregard something that may be potentially worrisome and not get evaluated," she noted. Pregnant women may not be aware that they should be concerned about irregular or changing moles.

Any changing mole—especially one that has become irregular or asymmetric—could be a melanoma. Synchronous and homogeneous darkening of multiple moles "is probably normal but still should be evaluated," she said. A delayed diag-

work-up (Semin. Oncol. 2000; 27:623-32).

Another analysis (Curr. Opin. Oncol. 1999;11:129-31) reports that the manufacturers and suppliers of interferon have "sparse data" on pregnant patients that suggest babies delivered to mothers receiving interferon therapy have low birth weights, Dr. Massry said.

She added that dacarbazine is considered the best treatment for pregnant patients with advanced disease.

► **What is the risk to the fetus in a pregnancy complicated by melanoma?** Transplacental metastases occur only in patients with hematogenous dissemination of melanoma. The incidence of maternal malignancy during pregnancy is 1 per 1,000, and melanoma accounts for 8% of all cancers during pregnancy.

"About 25% of the cancer that is metastatic to the parts of conception involve the fetus," Dr. Massry said. "Of cases with fetal involvement, 58% or so arise via melanoma."

At birth, she advised, "you want to do a thorough evaluation of the infant, a gross microscopic examination of the placenta, and [an examination of] the cord blood

buffy coat for tumor cells."

► **When can a woman safely become pregnant after treatment of melanoma?**

The commonly accepted advice is to avoid conception for 2-3 years if their lesions were 1.5 mm or smaller and 5-8 years if their lesions were greater than 1.5 mm. Part of this recommendation has to do with [when] most recurrences are likely to occur, she said. "If you're talking to a 20-year-old woman versus maybe a 40-year-old woman, the recommendations may change, depending on what their sense of urgency is" regarding childbearing.

Some investigators support the notion of individualized recommendations depending on tumor thickness, stage of diagnosis, age of the patient, and the desire of the patient to become pregnant (Cancer 2003;9:2130-3).

► **Is there a link between melanoma and use of oral contraceptives or hormone therapy?** Older studies suggest that high-dose oral contraceptives raise the risk of melanoma, but newer studies that include epidemiologic analysis refute the earlier data. For example, a controlled study of more than 2,000 women found no relationship between the incidence of melanoma and oral contraceptive use, age at onset of use, number of years used, or proximal relationship to use (Br. J. Cancer 2002; 86:1085-92).

Dr. Massry noted that there is "a paucity of information" on hormone therapy and melanoma. Some investigators maintain that there is no reason to withhold hormone therapy from a woman if it is otherwise recommended (Climacteric 2002;5:197-200). ■

DRUGS, PREGNANCY, AND LACTATION

New Asthma Treatment Guidelines

The 2004 asthma treatment guidelines for pregnant women, issued by the National Asthma Education and Prevention Program last month, is an extremely valuable document that meets a great need for guidance in this area. The guidelines, which also include a table on the stepwise approach to managing asthma in pregnancy, are the first to be issued on treating asthma in pregnant women in more than 10 years.

A better understanding of the inflammatory nature of the disease has promoted a major shift in therapy. Anti-inflammatory medications, most notably corticosteroids, and mast cell stabilizers (leukotriene inhibitors) are the first-line drugs of current treatment. Until 20 years ago, the hallmark treatment was theophylline. Although this agent is rarely used today to treat asthma, the guidelines say at recommended doses, it is safe during pregnancy.



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The authors of the document, a multidisciplinary expert panel, performed a systematic review of the available evidence on asthma treatment in pregnancy. Some of the key findings are:

► **Inhaled corticosteroids** can reduce the risk of asthma exacerbations and improve lung function. There is no evidence that inhaled corticosteroids are linked to adverse outcomes. When taken through the inhaled route, systemic exposure is much less than with oral corticosteroids. Budesonide has the most data backing its safety in pregnancy, making it the "preferred inhaled corticosteroid," according to the guidelines. But the document points out that there are no data indicating the other agents are unsafe in pregnancy.

► **Oral corticosteroids** may be necessary for treating women with severe asthma. While there are conflicting data on their safety in pregnancy, they may be warranted in women with severe disease, according to the guidelines. In the general population, there is an association between use of oral corticosteroids in the first trimester and an increased risk for cleft lip and/or palate, compared with nonuse (0.3% vs. 0.1%), but not many asthmatic pregnant women have been included in these studies.

This risk for oral cleft has been shown in animals and in humans. Our Motherisk Program systematically reviewed studies and found a two- to threefold increase in oral cleft (with first-trimester exposure), which probably is not the case for inhaled steroids because the systemic dose is much smaller. Clearly, patients who are prescribed oral corticosteroids in the first trimester should be informed of this risk.

During the second and third trimester, oral steroids cannot cause

malformations. However, there are studies, which do not include patients with asthma, indicating that systemic exposure to corticosteroids may be associated with some CNS damage in babies. Most of these data were from studies of premature infants whose mothers received corticosteroids to enhance lung maturation.

There is evidence that repeating the dose of corticosteroids more than once may increase the risk of adverse brain outcome in premature babies. If a woman needs high-dose corticosteroids late in pregnancy, such a possibility should be discussed with her before prescribing these agents.

► **The short-acting β_2 -agonist albuterol** is the preferred drug in this class for treating acute symptoms, and the available data on the safety of β_2 -agonists are reassuring, the guidelines say. Albuterol has been studied in many mil-

lions of patients worldwide and in thousands of pregnant women, and there is no indication whatsoever that it has any teratogenic effects. Since it is inhaled, systemic exposure is not great.

► **For women with persistent asthma** who are not well controlled on low-dose inhaled corticosteroids, increasing the dose or adding a long-acting β_2 -agonist is recommended, but there are not enough data indicating which approach is preferable, according to the guidelines. It is fair to say that β_2 -agonists have not been shown to be teratogenic.

► **Cromolyn**, used as a preventive treatment, appears to be safe, based on available evidence, the guidelines state.

► **Leukotriene modifiers**, as the document notes, have "minimal" data available on their use in pregnancy, although there are some reassuring animal data. We at Motherisk are prospectively collecting information on cases of pregnant women exposed to these drugs, and based on our experience, they do not appear to be major teratogens.

(A copy of the guidelines issued by the National Asthma Education and Prevention Program, which is administered by the National Heart, Lung, and Blood Institute, can be found at www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm.)

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nosis of melanoma in pregnant patients illustrates that physicians should treat changing nevi exactly the same in pregnant and nonpregnant patients, and biopsy the moles promptly.

No study has identified a difference in survival rates between pregnant patients with melanoma and nonpregnant, age-matched controls, but studies consistently show an increase in median thickness among pregnant patients with melanoma, compared with nonpregnant, age-matched controls. While a delay in melanoma diagnosis is the likely cause for this difference, Dr. Massry said that there are no data to confirm or refute the possible role of growth factors that induce thicker and more rapidly growing melanomas.

In her presentation, she also addressed the following questions related to melanoma:

► **How does one approach recurrent melanoma in pregnant patients with stage II-IV disease?** CT and x-ray can be used if the benefits and risks are discussed with the patient. One study supports the use of MRI in the systemic