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Journal

JAMA Dermatology, 141(5)

ISSN

2168-6068

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Publication Date

2005-05-01

DOI

10.1001/archderm.141.5.601

Copyright Information

Peer reviewed

Hormonal Effect on Psoriasis in Pregnancy and Post Partum

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Objectives: To investigate prospectively how psoriasis fluctuates in pregnancy and post partum and to correlate hormone levels in pregnancy (progesterone and estrogens) with psoriatic change.

Design: Psoriatic body surface area (BSA) in pregnant patients with psoriasis (study group) and nonpregnant, menstruating patients with psoriasis (control group) were assessed 5 times over a year. Hormone levels (progesterone and estrogens) were measured in the study group and correlated with change in BSA.

Setting: University-affiliated obstetric and dermatology clinics.

Patients: Forty-seven pregnant patients in the psoriasis group and 27 nonpregnant, menstruating patients in the control group.

Results: During pregnancy, 55% of the patients reported improvement, 21% reported no change, and 23% reported worsening. However, post partum, only 9% of patients reported improvement, 26% reported no change, and 65% reported worsening. Psoriatic BSA decreased significantly from 10 to 20 weeks' gestation ($P<.001$) compared with controls, whereas BSA increased significantly by 6 weeks post partum ($P=.001$) compared with controls. In patients with 10% or greater psoriatic BSA who reported improvement (n = 16; mean BSA, 40%), lesions decreased by 83.8% during pregnancy. There were significant or near significant correlations between improvement in BSA and estradiol ($P=.009$, $r=0.648$), estriol ($P=.06$, $r=0.491$), and the ratio of estrogen to progesterone ($P=.006$, $r=0.671$).

Conclusion: High levels of estrogen correlated with improvement in psoriasis, whereas progesterone levels did not correlate with psoriatic change.

Arch Dermatol. 2005;141:601-606

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Financial Disclosure: None.

ANECDOTAL REPORTS SUGgest that psoriasis tends to improve in pregnancy.[1] Prior studies examining psoriatic change in pregnancy (**Table 1**) have been retrospective, often with the patient completing the survey several years after her pregnancy. The objectives of this study were 2-fold: to investigate prospectively how psoriasis fluctuates in pregnancy and post partum and to correlate progesterone and estrogen levels in pregnancy with psoriatic change.

Pregnancy is associated with a substantial increase in the levels of estrogen and progesterone. There have been reports of patients taking high-dose estrogen oral contraceptives, who experience an improvement of their psoriasis[9] and psoriatic arthritis.[10] In contrast, psoriatic worsening has been reported when estrogen and progesterone levels drop post partum,[1,3,9,11] prior to menses,[9] and at menopause.[9] Most patients receiving hormone therapy around menopause noted no change in their psoriasis.[9]

Hormonal changes in pregnancy may play a role in improving psoriasis by promoting a state of immune tolerance. Estrogens have both immunosuppressive and immunostimulatory properties. Estrogens have been shown to stimulate B-cell–mediated immunity but to suppress T-cell–mediated immunity.[12] On the other hand, progesterone is primarily immunosuppressive. Progesterone down-regulates T-cell proliferative response[13-15] and has been shown to be the key factor in uterine immunosuppression.[16,17] Therefore, it had been postulated that high levels of progesterone would correlate with improvement of psoriasis.[1]

Three types of estrogens are produced in pregnancy: estradiol and estrone, from maternal and fetal androgenic precursors, and estriol, from fetal androgenic precursors.[18] Estradiol is the most potent of the natural estrogens, and estriol is the weakest.[18] Early in gestation, estradiol and estrone predominate, and later in pregnancy, estriol becomes the principal estrogen.[19] Because progesterone levels increase more dramatically

Table 1. Results of Prior Retrospective Studies: The Effect of Pregnancy on Psoriasis*

Source	No. of Women	Improved, %	Unchanged, %	Worsened, %
Lane and Crawford,[2] 1937	63	16	72	11
Lomholt,[3] 1963	70	38	57	4
Farber et al,[4] 1968	300	50	23	27
Braun-Falco et al,[5] 1972	85	40	40	17
Farber and Nall,[6] 1974	1018	32	50	18
Dunna and Finley,[7] 1989	65	39	42	12
Boyd et al,[1] 1996	90	63	23	13
Park and Youn,[8] 1998	85	42	39	19
Mowad et al,[9] 1998	46	35	46	18
Total	**1822**	37	44	18

*This table was adapted from Moward et al.[9]

Figure 1. Overview of the study participation period. Five times over the course of a year (represented by 5 arrows) a questionnaire was completed for study group and control group patients, and, for study group patients only, hormone levels were measured.

compared with estrogen levels, it has also been proposed that the change in the estrogen-progesterone ratio may also produce an altered immunity.[11]

METHODS

STUDY SUBJECTS

Forty-seven patients were enrolled in the study group, which consisted of women with psoriasis who were pregnant. Twenty-seven patients were enrolled in the control group, which consisted of nonpregnant menstruating women with psoriasis. There was no minimum amount of psoriatic body coverage required to be eligible for the study. All patients had stable plaque psoriasis diagnosed through physical examination by a dermatologist or the study coordinator, who received extensive training on how to diagnose psoriasis.

More than 1350 patients were screened for psoriasis at 5 obstetrics offices in Orange County and Long Beach, Calif, at their initial prenatal visit. Control group patients were recruited in dermatology offices in Orange County. Patients for the study and control groups were also recruited through the National Psoriasis Foundation Web site and mailings. The study was approved by the institutional review boards of the University of California, Irvine, and Long Beach Memorial Health Care Systems, and informed consent was obtained.

Out of the 47 study group patients, 36 were enrolled during pregnancy, with a mean week of enrollment at 17 weeks' gestation. The remaining 11 patients were enrolled after pregnancy but prior to 24 weeks post partum. Data collection occurred from July 2000 to May 2003. Because the patients were enrolled at a steady rate over the course of 2 years, it was thought that the effect of seasonal variation on psoriasis due to changing daylight patterns would be minimal. Only 1 patient did not complete the study because her baby was not yet born by May 2003.

STUDY DESIGN

Figure 1 depicts the study participation period for the study and control group patients. Patients were assessed 5 times over the course of a year: first, second, and third trimester at approximately 10, 20, and 30 weeks of pregnancy (P1, P2, P3, respectively) and 6 and more than 24 weeks post partum (P4 and P5, respectively). Controls were assessed at similar time intervals, as-
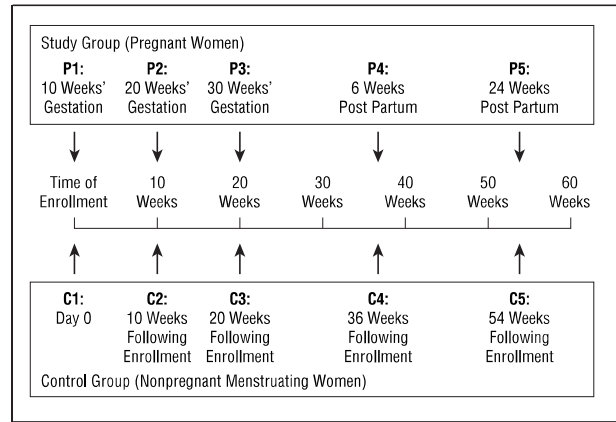
suming a 40-week gestation: initial enrollment, followed by 10, 20, 36, and 54 weeks after enrollment (C1, C2, C3, C4, C5, respectively). At each interval, patients completed a questionnaire detailing their current medications for psoriasis, their perceived stress level (score, 1-10), their perceived psoriasis severity (score, 1-10), breastfeeding habits (if applicable), and psoriatic body surface area (BSA). The psoriatic BSA was calculated using the "rule of nines" method. Each patient received instructions on how to perform the BSA calculation and also marked the areas covered with psoriasis on a diagram, as a means of visual confirming that the BSA calculation was reasonable.

Blood was drawn for hormone levels (estriol, estrone, estradiol, and progesterone) for 19 of the 47 study group patients (several patients wanted to participate in the questionnaire portion of the study but not the phlebotomy). Of these 19 patients, there were 5 possible blood draws (P1 to P5), which were occasionally not performed if the patient was unavailable to have blood drawn at the appropriate time. The serum hormone levels were determined by the following method: progesterone fluorescence immunoassay and estradiol fluorescence immunoassay (Tosoh Bioscience, South San Francisco, Calif); estriol fluorescence immunoassay (Perkin-Elmer Corp, Norwalk, Conn); and estrone radioimmunoassay (Diagnostic Systems, Webster, Tex).

STATISTICAL ANALYSIS

Reported values were treated as continuous, in the case of hormone levels and BSA, and as ordinal, in the case of psoriasis and stress scales. Data were analyzed using the Mann-Whitney test and the t test for paired and independent samples. Prior to performing t tests, distributions were examined and natural logs were taken to create a more normal distribution where necessary. Bivariate comparisons between 2 continuous measures were made with Pearson r, between continuous and ordinal measures with Gamma, between 2 ordinal measures with γ or Spearman ρ, and between 2 nominal measures with the Fisher exact test. The level of statistical significance was $P \leq .05$.

RESULTS

DEMOGRAPHIC DATA

The mean (SD) age of the study and control groups was 30.6 (5.0) years (range, 20-44 years) and 33.4 (7.3) years

(range 21-48, years), respectively. The mean (SD) time between age at the onset of psoriasis and age at enrollment for the study and control groups was 11.2 (7.9) years (range 0-29 years) and 17.3 (10.0) years (range 0-36 years). The study group was 66% white, 19% Hispanic, 13% Asian, and 2% black, compared with 81%, 11%, 4%, and 4%, respectively, for the control group. A family history of psoriasis was cited by 53% (25/47) of the study group and 37% (10/27) of the control group. There were no statistically significant differences in age at enrollment, race, and family history of psoriasis between the study and control groups.

At P5/C5, when the study group had returned to prepregnancy hormone levels, there was no significant difference between the BSA for the study group (mean [SE], 17.83% [3.53%]) and the control group (mean [SE], 19.60% [4.16%]). Of the control patients, 13 (48%) used systemic medications during the study period, including psoralen UV-A light treatments, methotrexate, cyclosporine, and biologic agents. Because all systemic medications for psoriasis are contraindicated in pregnancy, the use of systemic medications by the control group was significantly greater than the use by the study group ($t_{72}=-4.284$; $P<.001$).

CHANGE IN PSORIASIS: STUDY VS CONTROL

The body coverage distributions throughout the course of the study participation period are displayed in **Figure 2**. There was a statistically significant change in BSA of the study group from P1 to P2 ($t_{46}=3.959$; $P<.001$), indicating an improvement of psoriasis from 10 to 20 weeks' gestation. There was also a statistically significant change in BSA from P3 to P4 ($t_{45}=-3.457$; $P=.001$), indicating a worsening of psoriasis post partum. In contrast, there were no statistically significant changes in the psoriasis of the control group during the year-long study participation period (C1 to C5).

PSORIATIC CHANGE IN PREGNANCY

At approximately 30 weeks of pregnancy, the question "Did your psoriasis improve, not change, or worsen during pregnancy?" was posed to the study patients, and the results are displayed in **Table 2**. Twice as many patients reported an improvement of psoriasis (26/47 [55.3%]) than those who reported a worsening of psoriasis (11/47 [23.4%]). When we examined the actual psoriatic BSA change, defining "improvement" and "worsening" as a change of greater than 3% BSA and "unchanged" as a change equal to or less than 3% BSA, there were still twice as many patients who improved (14/47 [30.0%]) than who worsened (7/47 [15.0%]). This finding is consistent with previously reported studies listed in Table 1. When the data from the 9 retrospective studies were combined, approximately twice as many patients reported an improvement of psoriasis in pregnancy (37%) than those who reported a worsening in pregnancy (18%).

PSORIATIC CHANGE IN POST PARTUM

In contrast to pregnancy, post partum (P4) there was a 7-fold increase in the number of patients who reported
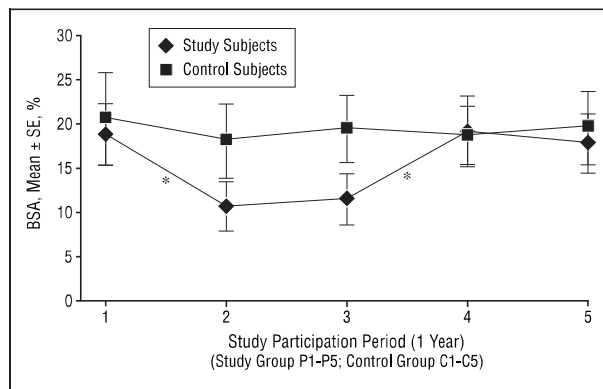
Figure 2. Psoriatic body surface area (BSA) in control and study groups at 5 assessments over the course of the study period (1 year). Only in the study group, the changes in BSA from P1 to P2 (10 to 20 weeks' gestation) and from P3 to P4 (30 weeks' gestation to 6 weeks post partum) were statistically significant ($P<.05$) (asterisks).

a worsening of psoriasis (30/46 [65.2%]) than those who reported an improvement of psoriasis (4/46 [8.7%]). When we examined the actual psoriatic BSA change, there were 6 times as many patients who worsened (19/46 [41.3%]) compared with the number who improved (3/46 [6.5%]). In the control group, the ratio of the patients whose psoriasis improved to the patients whose psoriasis worsened remained approximately the same over the 9-month period from C1 to C3 and from C3 to C4. Some of the control group patients were receiving active therapy accounting for the gradual improvement.

On average, the psoriatic BSA of the study group doubled between 30 weeks' gestation and 6 weeks post partum (n=46). It is interesting to note that the study group's increase in BSA post partum (P4) was not an increase to values greater than the BSA during the first trimester (P1). In other words, the "postpartum flare" previously described by patients anecdotally was really a return to the patients' baseline. This was further supported by statistically significant correlations of psoriatic BSA P1 with P4 ($r=0.791$; $P<.001$) and P1 with P5 ($r=0.461$; $P=.001$).

ACTUAL PSORIATIC BSA CHANGE IN PREGNANCY

The actual change of psoriatic BSA in pregnancy is displayed in **Figure 3**, which clearly depicts why there has been so much interest over the years in psoriatic improvement during pregnancy. The actual change in BSA of those who worsened in pregnancy (to the left of center) is significantly less than the change in BSA of those who improved in pregnancy (to the right of center). In a subgroup analysis of those with greater than 10% psoriatic BSA (n=16; mean BSA, 40%) at 10 weeks' gestation who reported improvement in pregnancy, the psoriatic lesions present at 10 weeks' gestation decreased substantially, on average 83.8% (29.4% SD; range, 20%-100%) by 30 weeks' gestation.

OTHER FACTORS

Neither the baby's sex nor breastfeeding habits correlated with the patients' psoriatic change. The month en-

Table 2. Psoriasis Fluctuation in Pregnancy and Post Partum

Results	Study Group		Control Group
	Pregnancy (P1 to P3) (n = 47)		**(C1 to C3) (n = 26):** I/N/W as Defined by Change in BSA (C3 − C1)*
	"Did Your Psoriasis I/N/W During Pregnancy?" (P3)	I/N/W as Defined by Change in BSA (P3 − P1)*	
Improved (I), % of patients	55	30	46
No change (N), % of patients	21	55	23
Worsened (W), % of patients	23	15	31
Ratio I:W	2.4	2.0	1.5
	Post Partum (P3 to P4) (n = 46)		Control Group **(C3 to C4) (n = 24):** I/N/W as Defined by Change in BSA (C4 − C3)*
	"Did Your Psoriasis I/N/W Post Partum?" (P4)	I/N/W as Defined by Change in BSA (P4 − P3)*	
Improved (I), % of patients	9	7	42
No change (N), % of patients	26	52	31
Worsened (W), % of patients	65	41	27
Ratio W:I	7.2	5.9	0.6

*"Improvement" and "worsening" were defined by a difference of greater than 3% body surface area (BSA) change. "No change" was defined as a change in psoriatic BSA between 3% and −3%.
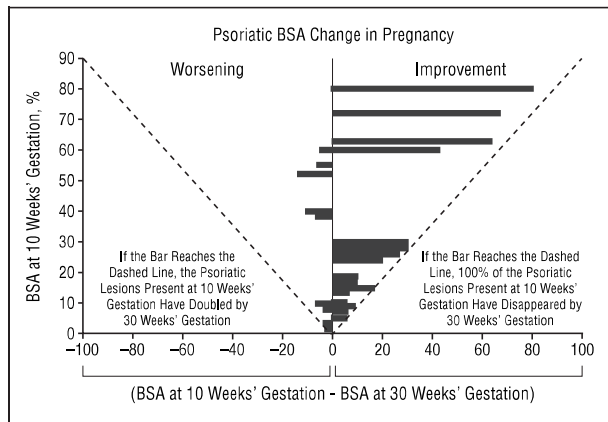

Figure 3. Psoriatic body surface area (BSA) change in pregnancy. Each black bar represents a patient's psoriatic body coverage change from 10 to 30 weeks' gestation. Positive values on the right represent improvement and negative values on the left represent worsening during pregnancy.

rolled did not correlate with the patient's psoriasis, supporting the fact that seasonal variation in sunlight exposure was negligible (data not shown). Mean (SD) stress levels on a 10-point scale were 6.0 (2.5), 5.8 (2.5), 5.6 (2.4), 6.9 (2.3), and 6.2 (2.1) from P1 to P5. The only significant increase in stress level was post partum from P3 to P4 (t_{45}=−2.935; P=.005), which was significantly associated with psoriatic body coverage change from P3 to P4 (γ=0.253; P=.03).

NORMAL HORMONE LEVELS

Values and variations in estrogen and progesterone levels in our study were consistent with previously described data for normal pregnancies.[18,20] Progesterone increased 200-fold (0.5-100 ng/mL), estradiol increased 24-fold (0.5-12 ng/mL), and estrone increased 6-fold (0.5-3 ng/mL). Estriol increased to 6 ng/mL on average.

CORRELATION OF HORMONE LEVELS AND PSORIATIC CHANGE

We used the third trimester hormone levels measured from 29 to 32 weeks' gestation to correlate hormone levels with psoriatic change. Because the levels of progesterone and estrogen are substantially lower in a nonpregnant state, the third trimester hormone levels are essentially equivalent to the delta estrogen and delta progesterone levels.

To correlate individual psoriatic improvement or worsening with hormone levels, we calculated the relative reduction of psoriatic BSA in pregnancy (R_{preg}, defined as [BSA at 10 weeks−BSA at 30 weeks]/BSA at 10 weeks' gestation). We performed this analysis on 2 groups: only those who had substantial psoriasis ($\geq$10% BSA) at the beginning of pregnancy (group 1, n=8) and all patients who had hormone levels measured between 29 and 32 weeks' gestation, including those with minimal psoriasis (group 2, n=15). **Figure 4** displays the results of the correlation between hormone levels and R_{preg} for all patients (group 2). The correlations were similar between group 1 and group 2. The correlation between estradiol and psoriatic change was near significant in group 1 (P=.08; r=0.651) and was significant in group 2 (P=.009; r=0.648). In both groups, there was a significant correlation between the estrogen-progesterone ratio and psoriatic change (group 1, P=.04, r=0.723; group 2, P=.006, r=0.671). There was a near significant correlation between estriol and psoriatic change in group 2 (P=.06; r=0.491). There were no correlations between estrone and progesterone levels and psoriatic change.

COMMENT

This study confirms prior data in greater detail, indicating that the number of patients with psoriasis who im-

prove in pregnancy is double the number of patients who worsen in pregnancy. It was previously suggested that progesterone, with its well-documented inhibition of T-cell activation and response, was most likely responsible for this improvement.[1] However, our findings indicate that increased estrogen levels, and especially increased levels of estrogen relative to progesterone, correlate with psoriatic improvement. Progesterone levels alone did not correlate with change in psoriasis. Thus, we can speculate that just as patients who experience an improvement of psoriasis achieve higher levels of estrogen relative to progesterone during pregnancy, the psoriasis of those who achieve lower levels of estrogen relative to progesterone will remain the same or potentially worsen.

In contrast to prior retrospective studies that examined psoriatic change in pregnancy with general descriptive terms, the present study design included a quantitative assessment of psoriasis. Because of the concern that patients would not be able to use the Psoriasis Areas Severity Index score accurately, the patients were trained to use the "rule of nines" to assess their psoriasis. The severity of psoriasis (a number from 1 to 10 that the patient assigned to describe how she felt about the state of her psoriasis) correlated significantly with the change in BSA at each interval (P1-P2, $\gamma = 0.462$, $P<.001$; P2-P3, $\gamma = 0.314$, $P=.01$; P3-P4, $\gamma = 0.593$, $P<.001$; and P4-P5, $\gamma = 0.554$, $P<.001$).

In pregnancy there is a shift from T_H1 to T_H2 immunity that promotes fetal survival by decreasing T_H1 responses involved in rejection of the fetus as an allograft.[21] As predicted from this immune deviation, autoimmune diseases categorized as T_H1 mediated (eg, psoriasis,[22,23] rheumatoid arthritis,[24-26] and multiple sclerosis[27-29]) have been shown to improve in pregnancy. Estrogen is a member of the superfamily of nuclear receptors for steroid hormones, vitamin D_3 (1,25-dihydroxyvitamin D_3), thyroid hormone, and retinoic acid. The apparent shift from T_H1 to T_H2 immunity described in research involving both estrogen and vitamin D_3 suggests the possibility that there exists a common mechanism among the members of the nuclear receptor superfamily that results in an improvement of T_H1-mediated autoimmune diseases such as psoriasis.[30-34]

We believe that further examination of how estrogen may improve psoriasis is warranted. Estrogens have been shown to improve rheumatoid arthritis[35-37] and multiple sclerosis.[38,39] In a recent clinical trial by Sicotte et al[39] of 10 patients with multiple sclerosis, 8 mg/d of estriol for 6 months (equivalent to estriol levels at 6 to 8.5 months of pregnancy) demonstrated significant decreases in delayed type hypersensitivity responses, interferon-γ levels, and gadolinium-enhancing lesions on monthly cerebral magnetic resonance images. Whether estriol can improve psoriasis or can prevent worsening of psoriasis in menopause should be explored.
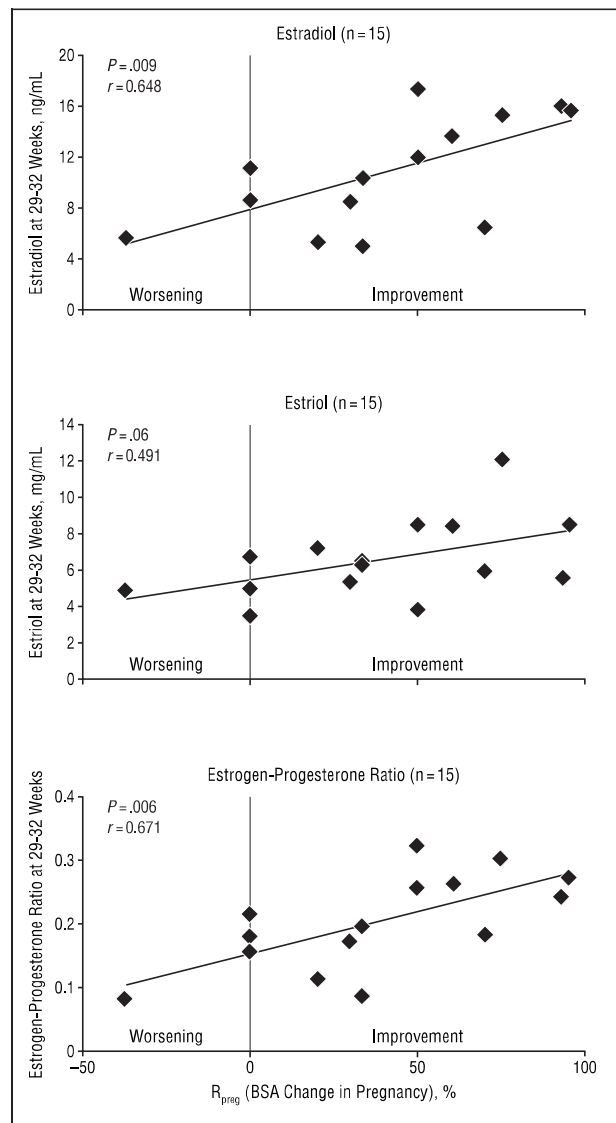
Figure 4. Correlation of hormone levels at third trimester and the relative reduction of psoriatic body surface area (BSA) in pregnancy (R_{preg}, defined as [10 week BSA−30 week BSA]/10 week BSA). 100% Indicates that all lesions disappeared during pregnancy, and −50% indicates that the lesions doubled.

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