The role of the skin biopsy in the diagnosis of atypical dermatoses of pregnancy.

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Abstract

Objectives: The aim of the study is to evaluate the benefits of skin biopsy in pregnant women complained of skin lesions during pregnancy.

Patients and methods: Women with pregnancy induced skin lesions were included in this prospective study, evaluated clinically by history and examination. Skin biopsy was performed between 28 and 39 weeks of pregnancy. Patients were classified according to the clinical diagnosis into two groups: typical and atypical dermatosis.

Results: One hundred ninety eight women with skin lesions during pregnancy were included. All patients underwent skin biopsy, 3 patients excluded from the study due to their abnormal coagulation profiles Based on skin biopsy results, The diagnosis of intrahepatic cholestasis was noted in 33 patients were diagnosed as eruption of pregnancy, 9 patients as pruritic folliculitis and 3 as pemphigoid gestations.

Conclusions: Routine skin biopsy should be used as a basic part of the work-up for women with atypical dermatoses of pregnancy.

Keywords: Skin biopsy, Dermatoses of pregnancy, intrahepatic cholestasis.

Introduction

Various physiological and pathological skin changes are common in pregnant women. The true diagnosis of these skin diseases are very important to avoid maternal and fetal complications during pregnancy [1,2]. Skin lesions with pregnancy can be pre-existing, human effect or pregnancy The dermatoses of pregnancy include Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP), Intrahepatic Cholestasis of Pregnancy (ICP), Pemphigoid Gestations (PG), and atopic eruption of pregnancy. [3].

Most of these conditions usually resolve at term or during puerperium, and do not carry any fetal risk and only require symptomatic treatment. In few cases of Prurigo of pregnancy, there is a risk of developing atopic skin changes in the infant. In patients with pemphigoid gestosis immunoglobulin G cross the placenta, and 5 to 10 percent of new-borns develop urticaria, vesicular or bullous lesions after delivery [4]. Intrahepatic cholestasis poses an increased risk of prematurity intrapartum fetal distress (22-33%) [5]. Premature delivery (19-60%) and stillbirths (1-2%) [6]. Therefore, early diagnosis, prompt treatment, and close obstetric surveillance are mandatory in these cases.

Although these disorders are all characterized by intense pruritus during pregnancy, they may be distinguished by timing, morphology and treatment. Clinical resources history and physical examination are the most important diagnostic clues. Most of cases are diagnosed by physical examination and clinical history [7]. On the other side, the rarity of these diseases, their variable clinical morphology, the lack of unequivocal diagnostic tests (with the exception of immunofluorescence in pemphigoid gestations) as well as limited treatment options have led to confusing terminologies and have made their diagnosis difficult.

Patients and methods

The current prospective cohort interventional study was conducted at Menofia university Hospitals, Egypt between January and December 2018. The study was approved by the Ethical and Research Committee of the Council of Obstetrics and Gynecology Department and dermatology department.

A minimum sample size of 196 patients was required to see 10 percent of dermatosis in them with a bond on error of 0.042 (4.2%) with a power of 0.8, an alpha significance level of 0.05 with a 95% confidence interval. Third trimester two

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hundred pregnant women were included in the study from the antenatal clinics all primi and multigravida in their third trimester was selected from the antenatal clinic during a period of twelve months. Patients with dermatosis flaring up or had physiological dermatosis were excluded from the study. The purpose of the study and the procedures were explained to all enrolled women and written informed consent was obtained from each participant. A comprehensive pro-forma was used to record all the relevant information.

Evaluation of the patients was done after obtaining consent in the form of full history, parity, gestational age, cutaneous eruption, duration, symptoms, and family history of any similar conditions during pregnancy. Clinical examination of the skin lesions in the form of area affected, eruption and blister formations

All patients in the study were pregnant in third trimester of pregnancy and divided in 2 groups either typical or atypical dermatosis Liver functions and complete blood count were done for patients presented with itching to exclude cholestasis of pregnancy.

Upon presentation to the dermatology department, all patients provided informed consent after being interviewed by a dermatologist. Skin biopsy for histopathology was done routinely. Sampling technique was probability non-purposive sampling. As a standard of care, all atypical skin lesions, identified by clinical examination and thus scheduled for biopsy, are routinely imaged and stored in a dedicated database. Selected patients underwent biopsy with images which were stored and then examined by microscope by dedicated lens At 10 fold magnification. More specifically, for each case a clinical overview, a close-up with a ruler and one dermoscopic image are collected. Clinical images are acquired using a Canon G15 (Canon Inc., Tokyo, Japan) and dermoscopic images.

The skin punch biopsy is an easy procedure that can be performed in a doctor's office by the physician. This procedure causes minimal pain and discomfort to the patient requiring no sutures, only an adhesive bandage. After the excision of a skin lesion, Referral form was filled by the dermatologist with clinical details mentioning of the area, site and clinical diagnosis. When the histopathologic report is rendered, the clinician reviews the case in light of the clinical pictures. Cases for which a good clinico-pathologic correlation is missing are jointly reviewed by the referral clinicians and the referral dermatopathologist combining all relevant clinical and histologic data including clinical images and a picture selection of histopathologic slides. A final consensus diagnosis is then reached in light of the case discussion

Statistical analysis

Data were analyzed using SPSS for Windows, version 15. Quantitative (numerical) variables have been presented as mean ± standard deviation (SD) values. Qualitative (categorical) data are presented in terms of number of cases and percentage. Analysis of numerical variables was performed using the independent Student's t test for normal distribution or Mann–Whitney U test for non-parametric data distribution (z value). Comparison of categorical data parameters was performed using Chi-square test or Fisher exact test.

Results

A total of 198 patients with dermatoses of pregnancy met our inclusion criteria. Patients ranged in age from 18 to 34 years. The mean age ± standard deviation SD at admission was 27.5 years±4.55. The mean body mass index was 31.3±7.42 kg/m2 (range 24-38 kg/m2). The median parity was 1.08±0.71 (range 0-4). Primi-gravidas comprised 63.7% of patients. The gestational age at the time of biopsy range 28 to 39 weeks (mean=34.21± 3.48). In 12 (6%) patients there was a history of cutaneous eruptions in previous pregnancies which had resolved within three months after the delivery. In all previous pregnancies, the fetal outcome had been normal (Table 1).

Baseline laboratory characteristics of the patients are recorded. The hyponatremia frequency was 24%. AST levels were mildly elevated in 5 patients. ALT levels were also mildly higher in 7 patients. On the other side, no patients had abnormal renal function tests (Table 2).

Amongst 198 patients with specific dermatoses, 82(41.41%) had prurigo of pregnancy, 71(35.85%) had dermatoses associated with intrahepatic cholestasis of pregnancy, and 33(16.66%) had polymorphic eruption of pregnancy. Pruritic folliculitis of pregnancy was observed in 2 patients and diagnosed by skin biopsy in 7 patients. During the study, no case of pemphigoidgestationis or atopic dermatitis can be diagnosed without skin biopsy (Table 3).

Table 1: *Demographic data of the two studied groups.*

Variables	Group A Typical Dermatosis (number = 132)	Group B Atypical Dermatosis (number = 66)	P value, (95% CI), Significance
Age (Years) Mean ±SD	26.7±5.3	28.2±4.2	0, (-2.13-,-1.5, -0.86-), Non-Significant
Parity [Mean ±SD]	1±1.4	1±2.1	1, (-1.26, -1, -0.7),- Non-Significant
Weight (Kg) Mean ±SD	89.6±7.2 Kg	94.1±6.7	0.08, (-5.5, -4.5, -3.5), Non-Significant
BMI (kg/m^2) Mean ±SD	30.4±4.3	32.1±5.3	0.9, (-2.39, -1.7, -1.0), Non-Significant
Gestational age at skin biopsy (Weeks) Mean ±SD	33.1±1.03	34.24±0.54	0, (-1.19, -1., -1.0), Non-Significant

BMI: Body Mass Index, **CI:** Confidence Interval, **NS:** Non-Significant, **SD:** Standard Deviation,

Test used: Student`s t Test

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Table 2: *Laboratory results of the two studied groups.*

Variables	Total (number = 198)	Group A Typical D (number = 132)	Group B Atypical D (number = 66)
Bile salts (meq/L) Mean ±SD	142.1±7.3	141.7±6.2	142.2±6.5
K (meq/L) Mean ±SD	4.2±1.67	3.9±1.4	4.3±2.1
AST (ng/ml) Mean ±SD	29.6±7.2 Kg	28.33±7.9 Kg	19.1±6.7
ALT (ng/ml) Mean ±SD	21.4±6.3	17.8±5.3	25.1±5.4
creatinine (ng/ml) Mean ±SD	63. ±15.07	57.43±12.3	64.24±9.54

Table 3: *Histological findings of the two studied groups.*

Variables	Total number = 198	Group A Typical Dermatosis (Nb = 132)	Group B Atypical Dermatosis (Nb = 66)
Prurigo of pregnancy	82 (41.41 %)	60 (45.45 %)	22 (33.33 %)
Intrahepatic cholestasis of pregnancy	71 (35.85 %)	45 (34.09 %)	26 (39.39 %)
Polymorphic eruption of pregnancy	33 (16.66 %)	25 (18.93 %)	8 (12.12 %)
Pruritic folliculitis	9 (4.54 %)	2 (1.51 %)	7 (10.60 %)
Pemphigoid Gestationis	3 (1.51 %)	0	3 (4.54 %)

Prurigo of pregnancy was found to be commonest dermatoses. It was diagnosed in 82(41.41%) patients. Twenty two were primigravida, all others were multigravida. In seven multigravida there was history of similar eruption in previous pregnancies with no foetal abnormality. Three patients presented with history of asthma since childhood. The lesions were extremely pruritic. On clinical examination 52 patients had erythematosus papules with excoriation marks present on extremities and abdomen. Eight patients had lesions also on buttocks along with abdomen. Skin biopsy was done in all these cases, but there were non-specific changes.

Dermatoses with ICP were diagnosed in 71 patients (35.85%). Forty five patients (63.38%) had typical clinical picture and they were diagnosed without skin biopsy. They all had history of similar eruption in previous pregnancies with normal delivery and a healthy baby. They presented with pruritus, which was more marked over palms and soles, and worsened at night time. The only cutaneous finding was excoriation marks involving different parts of body especially over abdomen. One patient presented with jaundice along with cutaneous eruptions. Laboratory findings revealed slightly elevated transaminase and alkaline phosphatase levels. Hepatitis B and C screening was negative. Ultrasonographic studies were normal in all these cases.

Polymorphic eruption of pregnancy was observed in 33(16.66%) patients. Twenty five(75.76%) had typical dermatosis. All of them were primigravida and eruption appeared in their third trimester. The most common symptom was pruritus, often leading to disturbed sleep patterns. Urticated papules and plaques initially started from abdominal striae and then slowly spread to the rest of the body involving chest, thighs and buttocks. The characteristic feature was sparing of periumbilical region, palms and soles. There was no mucosal involvement observed. Eight (24.24%) patients had atypical picture and diagnosed by skin biopsy. Skin biopsy findings showed epidermalspongiosis, papillary dermal oedoema and a perivascular inflammatory infiltrate with numerous eosinophils.

In the study only nine patients had pruritic folliculitis of pregnancy (4.54%). Only two patients can be diagnosed clinically. They were multigravida and there was no previous history of similar eruption. Small erythematous, follicular papules were initially observed on the abdomen and then spread to the legs. These lesions were extremely pruritic. Pus swab for culture revealed a sterile pustule.

During the study period, no case of pemphigoidgestationis can be diagnosed without skin biopsy.

Although 66.66% of the skin biopsies were considered inappropriate with findings confirming clinical diagnosis, 33.33% had different findings.

Discussion

The pregnancy-specific skin disorders are pruritic, inflammatory eruptions. In 1983, Holmes and Black proposed a classification of pregnancy-specific skin disorders, which included pemphigoid gestationis, polymorphic eruption of pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy [8]. In 1998, Shornick proposed the addition of intrahepatic cholestasis of pregnancy [9]. The current classification was proposed by Ambros-Rudolph et al. in 2006 on the basis of a large retrospective study of 505 patients, and includes four entities: pemphigoid gestastionis, polymorphic eruption of pregnancy, atopic eruption of pregnancy (encompassing prurigo of pregnancy and pruritic folliculitis of pregnancy), and intrahepatic cholestasis of pregnancy [10].

Despite frequent association of pregnancy with skin eruptions, there are few studies on the subject. Our study discussed the diagnosis of specific of pregnancy. We highlighted the importance of routine skin biopsy along with various other factors such as age, gestational age, parity of patients, and history of similar eruptions in their previous pregnancies, physical examination and family history.

It is essential that physicians should be aware of the normal skin changes and some specific changes during pregnancy in order to prevent the patient's stress, unnecessary investigations and treatments. Certain dermatoses are specifically seen in pregnancy or in the postpartum period. It is, therefore, important to recognise and appropriately manage these cutaneous disorders because of the risk of maternal or fetal complications.

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Our study showed that specific dermatoses were not rare among pregnant women. We compared the result of our study with various other national and international studies. Prurigo was frequently observed in contrast to other studies, where polymorphic eruption was commonest dermatoses. It is commonly observed in primigravidas. In contrast to other studies, prurigo of pregnancy was found to be the most common specific dermatoses. Excoriated papules were present predominantly on the arms and the legs. It can affect either primigravida or ultigravida. Patients in our study had history of similar eruptions in previous pregnancies.

Dermatoses with intrahepatic cholestasis were the second most common disorder. Two patients had family history of similar eruptions during pregnancy. It is important to investigate all patients of dermatoses with intrahepatic cholestasis thoroughly to exclude any other systemic illness. In other published studies, polymorphic eruption was the commonest pregnancy-associated dermatoses, while in our study it was the second most common dermatoses. All patients were primigravida. Lesions were initially localized to abdominal striae and then slowly spread to the rest of the body. Patients with pruritic folliculitis presented with generalised red follicular papules distributed on the abdomen and the limbs. These papules were extremely itchy.

The focus of our study was on specific dermatoses and did not address other physiological skin conditions. A similar study on the frequency of pregnancy dermatoses had been done by Muzaffar F et al in 1999. We included patients in their third trimester whereas they had included 140 pregnant females from all trimesters for any cutaneous eruption. Their emphasis was mainly on the dermatoses which flare up during pregnancy and also physiological skin changes observed during pregnancy. Prurigo of pregnancy was found to be the commonest dermatoses in our study group whereas in Samdani AJ's6 study, polymorphic eruption was the commonest dermatoses. It was present in 38.29% cases. There was no case of pemphigoid gestationis in our study, whereas in that study it was quite frequent with approximately 20% patients with specific dermatoses having it. Average age of patients with dermatoses was 22 years, whereas in our study the average age of patients with specific dermatoses was 30.2 years.

In response to the study conducted by Roger et al our study highlighted the various other aspects like association of dermatoses in previous pregnancies and our study is different in this aspect that they also extended their study to evaluate the pregnancy outcomes of these dermatoses. In their study, the commonest dermatoses was polymorphic eruption of pregnancy, which was present in 43.8% cases. Intrahepatic cholestasis was present in 38.6% cases, pemphigoidgestationis was in 12.3% cases, and whereas pruritic folliculitis was the rare dermatoses they observed in their study [11].

We also compared our results with an international study conducted in 1999 by Voughan Jones SA et al.16 The commonest dermatoses in their study, like earlier studies, were polymorphic eruption of pregnancy. In our study most of the women with prurigo were multigravida, while in the study of Voughan et al 33% women with prurigo of pregnancy were primigravida. In our study dermatoses with cholestasis was commonly observed in multigravida. They showed that the incidence of intrahepatic cholestasis was 75% in the third trimester and most of the patients were primigravida. In our study, all the patients with polymorphic eruption of pregnancy were primigravida, while in their study 55% were primiparous. In our study, pruritic folliculitis was observed in multigravida and their results showed that all patients with pruritic folliculitis were primigravida, and 86% of them presented in their third trimester. Another retrospective study on pregnancy dermatoses was done in March 2006 by Ambrose CM. This study had evaluated the frequency and clinical characteristics of pruritic dermatoses in pregnancy and to assess a rationalised classification. This study is different from our study in the sense that they did not even evaluate the specific dermatoses but they also inducted pregnant women with other pruritic conditions like eczema and atopic dermatitis. They included women in all the trimesters. In their study, polymorphic eruption of pregnancy was found to be the commonest dermatoses. It was present in 21.6% cases. Pemphigoidgestationis was observed in 4.2% cases, intrahepatic cholestasis of pregnancy was in 3% cases, and prurigo of pregnancy was in 0.8% cases, while pruritic folliculitis of pregnancy was observed in 0.2% cases. They studied eczema and other pruritic conditions which are not included in our study. Our study is different from this study because we focused only on specific dermatoses in the third trimester.

Our study highlighted the frequency of dermatoses that are unique to gravid state. Early detection and early management of specific dermatoses prevent maternal and foetal morbidity and sometimes mortality. Liver functions and complete blood count are important in diagnosis of intrahepatic cholestasis but clinical examination is the most important method of diagnosis of polymorphic eruption and prurigo of pregnancy.

There is significant difference between our study and most of the study as our study done in short time but other studies done in long time. We studied only patients in the third trimester so we can document these changes only happened in the third trimester.

Besides, our study did not highlight the outcome of the pregnancy. We did not study the fetal outcome of the pregnancy so we cannot predict or avoid the fetal complication of these skin changes. Other limitations of the study included limited external and internal validity. The study was done in one hospital; we should avoid that in the future to be done in multiple centers. Only one dermatologist examined all the patients in our study so no variability in the clinical results [12].

Conclusion

Routine skin biopsy should be used as a basic part of the work-up for women with atypical dermatoses of pregnancy. Carful clinical examination of skin lesions during the third trimester is the clue factor in diagnosis and referral to dermatologists is important with patients having normal liver functions and blood count.

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