

# The Skin Findings of Pregnant Women and Our Treatment Choices. A Turkish Experience: A 5-year Survey

*Gebelerde Görülen Dermatolojik Hastalıklar ve Bu Hastalarda Tedavi Tercihlerimiz. Türkiye'den Bir Deneyim: 5 Yıllık Bir İnceleme*

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## ABSTRACT

**AIM:** The number of pregnant women applying to dermatology outpatient clinics has increased. This has brought to notice the need for a specialized approach. In order to deal with pregnant women and their diseases, one must have a good knowledge of the skin disorders of pregnancy. Pregnant women and women who are considering pregnancy should be treated exclusively.

**METHODS:** Our aim was to evaluate the skin disorders of the pregnant women and to establish the treatment choices of dermatologists in our city when their patients were pregnant women.

**RESULTS:** Six hundred and ninety seven pregnant women who applied to the outpatient clinics were included in the study. Their diagnoses and the medications which are prescribed to them are retrospectively analyzed.

**Results:** Pruritus, urticaria, acne and contact dermatitis were the most common diagnoses. Mostly topical medications were prescribed by the dermatologists. Among the systemic therapies antihistamines, steroids and antibacterials were prescribed 195, 148 and 87 times respectively which account for almost 95.98% of all systemic medications.

**CONCLUSION:** Pregnancy is a unique period with a different range of dermatological diseases. It is also a vulnerable stage in terms of both the mother and the fetus. That's why the physicians generally choose topical therapies. Our study is an instructive one, showing the therapy preferences of dermatologists in our city when their patients are pregnant women.

**Key words:** dermatologic therapy; pregnancy; skin disorders

## ÖZET

**AMAÇ:** Son yıllarda dermatoloji polikliniğine başvuran gebe sayısı artmıştır. Bu da beraberinde bu hastalara özel bir yaklaşım zorunluluğunu getirmiştir. Gebe bir hastaya dermatolojik olarak yaklaşabilmek

için klinisyenlerin gebelikte görülen dermatolojik hastalıkları iyi bilmesi gerekmektedir. Gebeler ve gebelik düşüncesi olanlar ayrıcalıklı olarak gözden geçirilmelidir. Bu çalışmadaki amacımız gebelerde görülen deri hastalıklarını incelemek ve şehrimizdeki dermatologların bu hasta grubunda tercih ettiği tedavileri belirlemektir.

**YÖNTEM:** Kliniğimize başvuran 697 hasta retrospektif olarak değerlendirilmeye alındı. Bu hastalara verilen tanılar ve reçetelendirilen ilaçlar analiz edildi.

**BULGULAR:** Gebe hastalarda en sık görülen hastalıklar kaşıntı, ürtiker, akne ve kontakt dermatit olarak bulundu. Bu hastalara çoğunlukla topikal tedaviler reçete edilmişti. Sistemik tedavilerden en sık tercih edilenler antihistaminikler, steroidler ve antibakteriyellerdi. Bu sistemik tedaviler sırası ile 195, 148 ve 87'şer defa reçete edilmişti ve gebe hastalarda yazılan sistemik tedavilerin yaklaşık % 96'sını oluşturuyorlardı.

**SONUÇ:** Gebelik çok sayıda dermatolojik hastalığın görülmesi ile kendine özgü bir dönemdir. Aynı zamanda gerek anne gerek de fetus açısından çok hassas bir dönemdir. Bu nedenlerden dolayı doktorlar bu hasta grubunda genellikle topikal tedavileri tercih etmektedirler. Bu çalışma bölgemizdeki dermatologlarının gebe hastalarda tedavi tercihlerini göstermesi açısından yol göstericidir.

**Anahtar kelimeler:** deri hastalıkları; gebelik; dermatolojik tedavi

## Introduction

Pregnancy is a complex period due to hormonal, vascular, metabolic and immunological changes. Ninety percent of pregnant women experience a skin change of some kind or another<sup>1</sup>. These changes can be physiological or improval or worsening of existing dermatological conditions during pregnancy and dermatoses which are specific to pregnancy.

During pregnancy, the placenta acts like an endocrine organ and synthesizes estril and progesterone.

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Hypertrophy of the parathyroid glands causes decreased serum calcium levels. Such hormonal changes may play a part in the pathogenesis of certain skin diseases of the pregnancy<sup>2</sup>.

Immunological changes also occur during pregnancy. The T helper 1 (Th1): T helper 2 (Th2) cytokine ratio is shifted to the right, favoring the production of Th2 cytokines<sup>3</sup>. This tendency to the production of IL-4, IL-5, IL-10 and IL-13 seems to be necessary for the fetal survival. This shift is vital for the acceptance of foreign paternal antigens for the growth and development of the semi-allogeneic fetus<sup>4</sup>. Diseases like psoriasis that are mediated by Th1 cytokines tend to improve, while those mediated by Th2 cytokines, such as atopic dermatitis, may worsen. IL-4 also has an important role in the production of immunoglobulin E (IgE) by B lymphocytes and this is why atopic eruption of pregnancy develops<sup>5</sup>.

In recent years, the number of pregnant women applying to dermatology outpatient clinics has increased. This is due to health services being more readily available and socio-cultural improvement. This increase in the number of pregnant patients has brought to notice the need for a specialized approach. In order to deal with pregnant women and their diseases, one must have a good knowledge of the skin disorders of pregnancy. Pregnant women and women who are considering pregnancy should be treated exclusively.

One study reported that 68% of the 2752 pregnant women included, received at least one prescribed or non-prescribed medication during pregnancy<sup>6</sup>. Considering that both the mother and the fetus are vulnerable to the hazardous effects of medications, physicians must be familiar with the potential effects of certain drugs on the developing fetus and the mother. Because of their not having a good command of the subject, many physicians prefer not to prescribe any drugs during the pregnancy period. Another explanation for their not prescribing drugs is that they think that the most common dermatologic problems do not require urgent treatment.

After the catastrophic effects of thalidomide and diethylstilbestrol use in the Fifties and Sixties, international pregnancy risk classifications for medications were established. The United States Food and Drug Administration (FDA), the Swedish Catalogue of Approved Drugs (FASS) and the Australian Drug Evaluation Committee (ADEC) are just a few of these.

Although FDA classifications are the most widely used, other sources like Teratogen Information Service and Reproductive Toxicology Service data may be more up to date<sup>7</sup>.

Based on all this information, epidemiological research focusing on skin diseases in pregnancy would be a suitable approach to pregnant women and their dermatologic problems.

## Material and Method

Pregnant women who applied to our hospital's Dermatology and Venereology Outpatient Clinic between February 2010 and February 2015 were included in the study. The ages and dermatological diagnosis of the patients were recorded using the hospital's automation system. In order to ensure a proper diagnosis, dermatological inspection, laboratory tests, and if necessary, skin biopsies were performed. In case of multiple diagnoses in a single pregnant woman each diagnosis was evaluated separately. Any individual who visited the hospital a few times with the same diagnosis was counted once. The patients were evaluated under certain dermatological disease groups. These disease groups were as follows: pigmentary disorders, vascular disorders, hair disorders, nail disorders, striae distensae, scabies, urticaria, drug eruptions, psoriasis, contact dermatitis, atopic dermatitis, seborrheic dermatitis, acne, rosacea, systemic lupus erythematosus, bacterial infections, fungal infections, viral infections, intertrigo, recurrent aphthous stomatitis/Behçet's disease, unguis incarnatus, vasculitis, pruritus, xerosis, specific pregnancy dermatoses and others. Subgroups of specific pregnancy dermatoses were also separately evaluated.

As the second part of the study, we analyzed the medications that were prescribed by dermatologists in our region to pregnant patients. For this purpose, our hospital's data management system and the Ministry of Health's Pharmacy Data Management System (Medulla<sup>®</sup>) were used.

## Results

Six hundred and ninety seven pregnant women who were hospitalized or visited our outpatient clinics were included in the study. Their ages varied between 17 and 38, with a mean of 24.63. The total number of diagnoses given to these 697 patients (after omitting

repetitive diagnosis for the same individual) was 937. Eighteen patients were given three diagnoses and 204 patients were given two different diagnoses. Four hundred and seventy five patients were given only one diagnosis.

The dermatological diseases, number of patients with each diagnosis and ratios are listed in Table 1. Pruritus was the most frequent diagnosis with a ratio of 8.86% followed by urticaria (72 patients, 7.68%). Acne and contact dermatitis were the most frequent third and fourth diseases with ratios of 6.51% and 6.30% respectively. Other forms of dermatitis such as atopic dermatitis, seborrheic dermatitis and unspecified dermatitis make up a group of 107 patients, which is nonignorable.

The total number of drugs prescribed to these 697 pregnant women that we were able to have access to was 3184, including moisturizers and magistral drugs. The most frequently prescribed topical and systemic drugs are listed in Table 2 and Table 3. Not surprisingly, mostly topical medications were preferred. Moisturizers and topical steroids were, by far, the most frequently prescribed topical drugs. Magistral drugs were prescribed 397 times. Topical antifungals and antibacterials followed these three, at 193 and 179 times respectively.

Antihistamines were the most frequently prescribed systemic drugs followed by systemic steroids and antibacterials. These three groups were prescribed 195, 148 and 87 times respectively which accounts for almost 95.98% of all systemic medications.

## Discussion

Pregnancy is a critical period with a lot of physiological changes and vulnerability to various dermatoses. Due to various hormonal, vascular, metabolic and immunological changes, some diseases are more frequently observed whereas the others are less observed. Similarly some preexisting dermatoses heal whereas others worsen during the pregnancy period. The course of many other diseases is unpredictable.

In our study 8.86% of the pregnant women had non-specific pruritus. Wong et al. reported that this ratio could rise to 20%<sup>8</sup>. In another study by Shanmugam et al. this ratio was 4.6%<sup>9</sup>. Pruritus is mostly caused by dry skin but it can also be an early sign of nonspecific and specific pregnancy dermatoses. Since pruritus can be a forerunner of some dermatoses, pregnancy specific

**Table 1.** Dermatological diseases and their frequencies

Dermatological diseases	Number of patients / ratio
Pigmentary disorders	48 / 5.12%
Vascular disorders	16 / 1.71%
Hair disorders	45 / 4.80%
Nail disorders	21 / 2.24%
Striae distensae	37 / 3.95%
Scabies	9 / 0.96%
Urticaria	72 / 7.68%
Drug eruptions	14 / 1.49%
Contact dermatitis	59 / 6.30%
Atopic dermatitis	30 / 3.20%
Seborrheic dermatitis	34 / 3.63%
Psoriasis	30 / 3.20%
Systemic lupus erythematosus	9 / 0.96%
Acne	61 / 6.51%
Rosacea	27 / 2.88%
Bacterial infections	29 / 3.10%
Fungal infections	32 / 3.42%
Viral infections	15 / 1.60%
Unguis incarnatus	14 / 1.49%
RAS/Behçet's disease	30 / 3.20%
Intertrigo	29 / 3.10%
Vasculitis	12 / 1.28%
Pruritus	83 / 8.86%
Xerosis	54 / 5.76%
Specific pregnancy dermatoses	18 / 1.92%
Dermatitis nonspecified	43 / 4.59%
Others	66 / 7.05%
Total	937 / 100%

or nonspecific, a detailed history taking, proper physical examination and necessary laboratory studies are obligatory.

Inflammatory skin disorders, including contact dermatitis, atopic dermatitis, seborrheic dermatitis and psoriasis, affected 153 pregnant women. Pregnancy is a period of reduced cellular immunity and reduced production of Th1 cytokines such as IL-2, IFN- $\gamma$  and IL-12<sup>10</sup>. For this reason one would normally expect to see

**Table 2.** Topical agents prescribed to pregnant women

Topical agent	Total number prescribed
<b>Topical steroids</b>	673
- Weak potent	210
- Medium potent	258
- Potent	121
- Superpotent	84
<b>Antifungals</b>	193
- Azoles	90
- Terbinafin/butenafin	92
- Other antifungals	11
<b>Antibacterials</b>	179
- Mupirocin	74
- Fucidic acid	61
- Other antibacterials	44
<b>Antivirals</b>	57
<b>Topical antihistamines</b>	89
- Diphenhydramine	47
- Mepyramine	42
<b>Moisturizer</b>	813
- Urea	612
- Other moisturizers	201
<b>Calcineurin inhibitors</b>	93
- Tacrolimus	52
- Pimecrolimus	41
<b>Calcipotriol</b>	138
<b>Permethrin</b>	9
<b>Benzoyl peroxide</b>	57
<b>Azelaic acid</b>	38
<b>Magistral drugs</b>	397

**Table 3.** Systemic agents prescribed to pregnant women

Systemic Drug	Number of prescriptions
<b>Systemic steroids</b>	148
- Prednisolone	87
- Fluocortolone	48
- Betametasone	13
<b>Antihistamines</b>	195
- Diphenhydramine	7
- Chlorpheniramine	0
- Hydroxyzine	19
- Cetirizine	32
- Loratadine	11
- Levocetirizine	33
- Desloratadine	29
- Ebastine	5
- Pheniramine	42
- Rupatadine	17
<b>Antibacterials</b>	87
- Penicillin	59
- Cephalosporines	18
- Azithromycin	10
<b>Antifungals</b>	0
<b>Antivirals</b>	0
<b>Lidocaine</b>	8
<b>Biologic agents</b>	5
- Infliximab	5
<b>Cyclosporine</b>	5

contact dermatitis and psoriasis less than atopic dermatitis due to the fact that Th2 cytokines such as IL-4 and IL-10 dominate in the pregnancy period. IL-4 increases IgE generation by the B lymphocytes causing atopic eruption. However in our study 59 patients had contact dermatitis, which was almost double the incidence of atopic dermatitis which affected 30 individuals. This was an unexpected finding.

Vulvovaginal candidiasis is a common pathology in the pregnancy period. It is also caused by suppressed cellular immunity. Another reason for this is that high

levels of estrogen cause an increase in the vaginal glycogen level which creates a suitable media for candidal growth<sup>11</sup>. Briggs et al. reported that vulvovaginal candidiasis is seen in almost 15% of all pregnant women<sup>12</sup>. However in our study this ratio was only 3%. This might be due to the fact that vulvovaginal candidiasis was, possibly, treated by gynecologists.

The incidence of all infections throughout pregnancy is 25%<sup>12</sup>. In our experience this was almost 8% including vulvovaginal candidiasis. Herpes simplex virus (HSV) was seen in 2% of pregnant women<sup>13</sup>. Only three of our

patients had HSV infection. This discordance came to our attention. Again, we thought that some pregnant women could have been treated by gynecologists, internal diseases specialists or family doctors.

Hyperpigmentation is a common problem in many pregnant women. It is due to increased levels of estrogen, progesterone and melanocyte stimulating hormone (MSH). Estrogen and progesterone increase melanin secretion from the melanocytes<sup>14</sup>. Melasma is the most common form of hyperpigmentation, especially in women with darker skin. In our experience 40 pregnant women had melasma (4.27%). Barankin et al. reported that 45% of pregnant women had had melasma<sup>15</sup>. Pregnant women in Turkey are exposed to sunlight in almost every season of the year and melasma is a common skin condition. For this reason, pregnant women might have accepted melasma as normal. This may explain the low ratio.

Estrogen prolongs the anagen phase of the hair cycle and decreases the transition from anagen to telogen<sup>4</sup>. Its clinical manifestation is hypertrichosis which was observed in 3.6% of our patients. One should remember that, in contrast, in the postpartum period compensatory telogen effluvium is observed and can continue from six to twelve months<sup>2</sup>.

Striae are one of the most disturbing changes seen in pregnancy. They are seen in approximately 90% of pregnant women. They can be seen because of physical stretch or intradermal tears of collagen<sup>2</sup>. Only 3.95% of our patients complained about striae, which was much less when compared with the literature. Based on this, it can be said that, striae are not accepted as troubling by Turkish women or seen as a worthwhile reason for applying to a hospital.

Pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy and atopic eruption of pregnancy make up a group of diseases which are specific to the pregnancy period and are called the specific dermatoses of pregnancy. These were seen in 5% of 1430 patients in one study<sup>16</sup>. Only 1.92% of our patients were given one of these diagnoses. Possibly some patients who were given the diagnosis of pruritus and atopic dermatitis must have been categorized in this group, as many of the specific pregnancy dermatoses may start with nonspecific pruritus.

When we reviewed the prescriptions given to these pregnant women, as expected, we encountered mostly topical choices. As pregnancy has many mysteries, it

seems to be rational to be protective and minimalist when prescribing a medication. Therefore many physicians are unwilling to prescribe medications to pregnant women. However, a multinational survey indicated that 86% of pregnant women took an average of 2.9 medications throughout their pregnancy<sup>17</sup>.

Apart from moisturizers, steroids were the most commonly prescribed topical agents. Generally weak potent and medium potent ones were chosen. Topical steroids are accepted as safe during pregnancy, with a few exceptions. Chi et al. indicated that the use of more than 300 grams of potent and ultra-potent topical steroids throughout pregnancy can cause low birth weight in infants<sup>18</sup>. Furthermore, they proposed a guideline for topical steroid use in pregnancy in 2011<sup>19</sup>.

Topical antifungals and antibacterials were prescribed to 193 and 179 pregnant women respectively. Terbinafine and imidazoles were equally chosen. Considering that terbinafine is a category B drug and imidazoles are category C<sup>20</sup>, one would have expected to see terbinafine prescribed more. As topical antibacterials, mupirocin and fusidic acid, both category C<sup>20</sup>, were most commonly chosen.

Generally topical antihistamines are not chosen by dermatologists because of their potential to cause irritation<sup>2</sup>. However, in our study we observed that topical diphenhydramine and mepyramine were prescribed 47 and 42 times respectively. This may be a reflection of the fear to prescribe systemic agents.

For the treatment of acne, mostly azelaic acid (B), benzoyl peroxide (C) and magistral drugs were chosen (Table 2).

Among the systemic drugs, antihistamines, steroids and antibacterials were prescribed 195, 148 and 87 times respectively. Antihistamines are among the most commonly used drugs in pregnancy. Older, first generation ones are better studied with more data. There are contradictory reports about antihistamine use in pregnancy. A large number of pregnancies exposed to first generation antihistamines have been studied, and no definitive increased teratogenic risk was observed<sup>20</sup>. However, there are reports indicating fetal hypoxia with diphenhydramine, fetal eye and ear defects with chlorpheniramine<sup>21</sup>, and hypospadias with loratadine use<sup>22</sup>. Zierler, in 1986, reported that the use of antihistamines within two weeks of delivery caused a twofold increase in retrolental fibroplasias<sup>23</sup>. One recent study indicates that maternal antihistamine use increases the

risk of congenital heart defects<sup>24</sup>. Chlorpheniramine and hydroxyzine are the best two choices<sup>2</sup>. From the second generation antihistamines, cetirizine and loratadine can be safely used after the first trimester<sup>2</sup>. In our study more than half of the antihistamines prescribed to pregnant women were second generation ones. Although these new antihistamines seem to be safe, there are insufficient data about them being used in pregnancy.

In the placenta, prednisone and prednisolone are enzymatically inactivated. For this reason, they are the first choices in case of systemic steroid necessity<sup>20</sup>. In our study prednisolone and flucortolone, both category C drugs, were the most commonly prescribed systemic steroids. Although widely used during pregnancy, systemic steroids are thought to have the potential to cause orofacial clefts, premature delivery, intrauterine growth retardation, gestational diabetes, hypertension and preeclampsia<sup>25</sup>. For this reason, physicians must be careful when prescribing them.

Penicillins, cephalosporins and azithromycin were the systemic antibiotics prescribed to pregnant women in our study. All are considered compatible with pregnancy<sup>25</sup>.

We realized that neither antifungals nor antivirals were prescribed systemically to our patients. Considering that terbinafine and acyclovir are category B drugs<sup>20</sup>, this attitude can be accepted as overprotective. Another possible explanation is “lack of knowledge”

Among the biologic agents, only infliximab was given to five pregnant women. As these agents are new, there is a lack of data at present. There are reports about etanercept causing spontaneous abortion, vertebral anomalies, anal atresia, cardiac anomalies, skeletal anomalies and cardiac anomalies in animal models when used in pregnancy<sup>26</sup>. Thus, physicians should avoid prescribing these agents to pregnant women if there is an alternative.

Cyclosporine is a category C immunosuppressive agent. It has been used and studied in pregnant organ transplant recipients for a long time<sup>27</sup>. No birth defects have been attributed to it. Therefore it can be used in cases of resistant psoriasis and atopic dermatitis<sup>6</sup>. Despite this fact only five of our patients were prescribed systemic cyclosporine.

As a limitation, the number of patients included in the study can be considered as insufficient. Another limitation is that, as a diagnostic tool for epidemiology, health

management and clinical purposes, The International Classification of Diseases version 10 (ICD-10) is used in our country. Whether or not patients' records are accurately and fully documented using the ICD-10 system is also uncertain. Furthermore, there are still diseases which are not categorized in the ICD-10 system.

## Conclusion

When we review the literature about pregnancy and dermatological diseases, we generally come across the specific dermatoses of pregnancy. There are only a few reports about the dermatological diseases seen in pregnant women that are not specific to pregnancy. In this respect our study seems to be an illustrative one. Although limited to a certain region of the country, this study is also instructive, showing the therapy preferences of dermatologists in our region when their patients are pregnant women.

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