PREGNANCY AND SKIN

Editors
Sanjeev Gupta
Rohit Batra
Mudita Gupta

Forewords
Dedee F Murrell
Jenny Murase

JAYPEE

Contents

CHAPTER 1

Immuno-Hormonal Changes in Pregnancy

Mudita Gupta, Sanjeev Gupta

"Everything grows rounder and wider and weirder, and I sit here in the middle of it all and wonder who in the world you will turn out to be."

—Carie Fisher

INTRODUCTION

Pregnancy is the remarkable journey where a fertilized egg develops into a fetus within the mother's womb, typically lasting around 9 months. To nurture this semiforeign fetus, the mother's body undergoes a carefully orchestrated series of adjustments. These adaptations go beyond anatomical changes, like the growing uterus and breasts. They encompass metabolic shifts (for nutrient supply), immunological tuning (to prevent fetal rejection while safeguarding the mother from infections), and hormonal changes (play a maestro role, coordinating these physiological changes throughout pregnancy). All these physiological changes work in harmony to optimize the health of both the mother and the developing fetus.

HORMONAL CHANGES

Hormones play a critical role in maintaining pregnancy and supporting fetal development. The interplay of various hormones ensures the proper physiological changes needed for a successful pregnancy. Endocrine environment of pregnancy is complex and involves various hormones. Human chorionic gonadotropin (hCG), progesterone, estrogen, prolactin, relaxin, oxytocin, and human placental lactogen (hPL) are the principal hormones of pregnancy.

Human Chorionic Gonadotropin

Human chorionic gonadotropin is a crucial hormone in pregnancy. Initially produced by the blastocyst, hCG can be detected in the mother's blood and urine

as early as 11 days after conception. Following implantation, hCG levels double approximately every 2–3 days, peaking by the end of the first trimester (25.7×10^3 to 288×10^3 mIU/mL). In the second trimester, these levels begin to decline and then plateau (1.2×10^3 to 55×10^3 mIU/mL), further decreasing in the third trimester to levels lower than those at the beginning of the first trimester (1.1×10^3 to 56×10^3 mIU/mL) **(Fig. 1)**.

Human chorionic gonadotropin has following major actions:

- hCG supports pregnancy by maintaining the corpus luteum for progesterone production, stimulating fetal gonadal development, modulating the maternal immune response to protect the fetus, and promoting the development of placental blood supply.
- Additionally, hCG is linked to increased hormonal activity, contributing to breast tissue growth, morning sickness, stimulation of thyroid function, and production of inhibin and relaxin by the corpus luteum.

- Pregnancy heralds a cascade of hormonal transformations crucial for maternal health and fetal development
- hCG, progesterone, estrogen, hPL, prolactin, and relaxin are the six hormones which help in maintenance of pregnancy, maternal adaptations, and fetal growth
- hCG is the first hormone to appear and opens the door to rest of the hormonal changes in pregnancy
- hCG is responsible for supporting early pregnancy
- Morning sickness seen in early pregnancy is due to hCG

Progesterone

Progesterone is initially secreted by corpus luteum but after 10 weeks this function is taken over by placenta. Throughout gestation, progesterone levels exhibit a steady rise. In the first trimester, they elevate from approximately

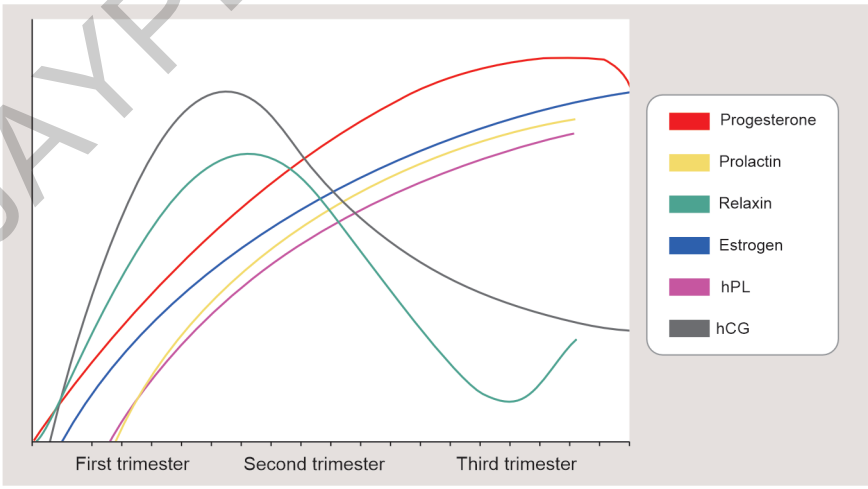

FIG. 1: Trends of various hormones in pregnancy.

(hCG: human chorionic gonadotropin; hPL: human placental lactogen)

10–30 ng/mL to 30–50 ng/mL. This upward trend continues into the second trimester, reaching levels between 25 and 90 ng/mL, and culminates in the third trimester with a peak range of 100–200 ng/mL. Progesterone level falls immediately before delivery.

Progesterone plays a pivotal role in pregnancy by maintaining the uterine lining, mitigating uterine contractions to prevent premature labor, fostering placental development, modulating the maternal immune response to safeguard the fetus, and facilitating breast tissue growth in readiness for lactation. Progesterone is responsible for various physiological dermatological changes in pregnancy, e.g., hyperpigentation, acne, and vascular changes (e.g., pregnancy glow, spider vein, and varicose vein). It also prolongs anaphase of hair.

- Progesterone secretion by placenta starts at 10 weeks and levels rise exponentially till immediately before term
- Progesterone is crucial for maintaining the uterine lining, preventing premature labor, and supporting breast tissue growth for lactation
- Progesterone is responsible for various dermatological physiological changes

Estrogen

Estrogen production in pregnancy originates initially from the maternal ovaries, adrenal glands, and peripheral conversion. In the early stages of the first trimester, estrogen levels hover around 0.3 ng/mL until reaching a gestational age of 6–10 weeks, after which they steadily escalate until term (2–30 ng/mL).

- Estrogen levels keep on increasing till term
- Estrogen exists in three different forms-of which estradiol is the most potent
- Estrogen promotes uterine and placental growth, regulates other hormones, and supports cardiovascular and breast tissue development

Three distinct types of estrogen operate during pregnancy: (1) Estradiol (E2), (2) estrone (E1), and (3) estriol (E3). Among these, estradiol stands out as the most potent. Estrone exists in relatively minor quantities and can also derive from androstenedione in adipose tissue. Estriol emerges as the predominant estrogen during pregnancy, synthesized by the placenta from 16-hydroxydehydroepiandrosterone sulfate (16-OH DHEAS).

Throughout pregnancy, estrogen assumes a myriad of roles, including the promotion of uterine and placental growth, regulation of other hormonal processes, initiation of breast tissue development for lactation, and facilitation of cardiovascular adaptations to meet the augmented demands imposed by fetal growth.

Prolactin

Increased estradiol leads to increase of prolactin which is ten times nonpregnant state. Prolactin levels rise progressively throughout pregnancy, starting in the first trimester and peaking in the third trimester, preparing the body for lactation. Prolactin's primary functions include stimulating mammary gland development

and milk production, regulating immune tolerance to the fetus, influencing maternal behavior, and adjusting metabolic processes to support breastfeeding. Prolactin rises from a nonpregnant level of 25 µg/mL to up to 400 µg/L.

- *Prolactin* prepares the body for lactation by stimulating mammary gland development and milk production, and it also regulates immune tolerance to the fetus
- *hPL* and other hormones such as *relaxin* and *oxytocin* modulate maternal metabolism, support cardiovascular adaptations, and prepare the body for labor and breastfeeding
- In addition to anatomical, metabolic, hematological alterations, these hormones modify maternal immunological response

Human Placental Lactogen

Human placental lactogen is also known as human chorionic somatomammotropin (hCS). hPL production starts at fifth week of gestation and continuously rises thereafter. This hormone is responsible for increasing insulin-like growth factor-1 and modulates maternal metabolism to ensure a steady supply of glucose and amino acids to the fetus. It increases lipolysis leading to more availability of free fatty acids for mother hormone responsible for insulin resistance in the mother, increasing blood glucose levels for fetal use. It also has growth hormone-like and prolactin-like action.

Relaxin

Relaxin is a hormone crucial for human pregnancy, with levels peaking in the first trimester and follows hCG pattern, stabilizing at elevated levels throughout gestation. It facilitates cervical ripening, reduces uterine contractility to prevent premature labor, and promotes the growth and remodeling of reproductive tissues. Additionally, relaxin aids cardiovascular adaptations by increasing cardiac output and renal function, and it helps loosen joints and ligaments in the pelvis for childbirth. Its role in angiogenesis supports increased blood flow, essential for both maternal and fetal health.

Androgens

There is a progressive increase of testosterone with pregnancy. This increased androgen is produced by maternal ovary, both maternal and fetal adrenal glands. Pregnant female is protected from signs of hyperandrogenism because of increased production of sex hormone-binding globulin (SHBG) by liver during pregnancy leading to no change in free testosterone in first and second trimester **(Fig. 2)**. But there may be increased testosterone in third trimester. Testosterone in the presence of aromatase produced by placenta gets converted into estrogen thus preventing hyperandrogenism during pregnancy.

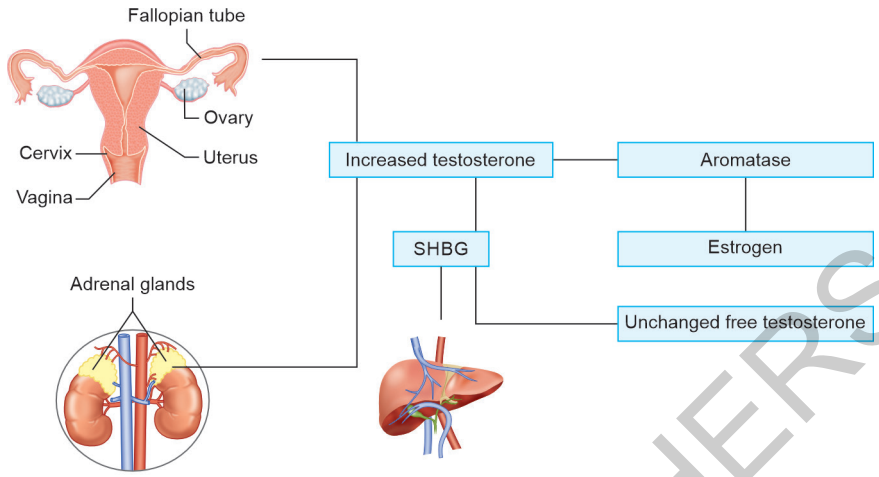

FIG. 2: Testosterone production and prevention of hyperandrogenism.
(SHBG: sex hormone-binding globulin)

Oxytocin

Increased production of oxytocin by posterior pituitary in third trimester helps in induction of labor.

Other Hormones

During pregnancy, there is a hypercortisolism (three times nonpregnant state) due to increase in production of cortisol, adrenocorticotropic hormone (ACTH), corticosteroid-binding globulin (CGB), and deoxycorticosterone. Progesterone has antiglucocorticoid action which balances this hyper cortisone activity.

Reduced vascular resistance and blood pressure lead to increase aldosterone production.

Stimulating effect of hCG in first trimester lead to decrease in thyroid-stimulating hormone. In second trimester, estrogen leads to increases production of thyroid-binding globulin which leads to increased levels of thyroxine (T4) and triiodothyronine (T3). But overall pregnancy is a euthyroid state. Parathyroid hormone secretion also increases leading to increased predisposition of hypocalcemia in conditions like pustular psoriasis of pregnancy. There is also a significant increase in insulin-like growth factor binding protein-1 (IGFBP-1), peaking at second trimester with a slight rise again near term.

PHYSIOLOGICAL IMMUNE SYSTEM CHANGES

Why the mother does not reject a fetus which is semi-allogeneic? Is pregnant female immunocompromised? Recent research reveals that maternal-fetal

interface is not immunologically inert but possesses a series of active immune processes to sustain balance of the maternal-fetal tolerance and antipathogen defense. An alteration of this intricate balance may lead to either preterm births, abortion, preeclampsia or TORCH (toxoplasma, rubella, cytomegalovirus, herpes/hepatitis/human immunodeficiency, varicella, parvovirus b19, syphilis) or some other infections.

Immunological Tolerance Mechanisms

Mother's immune system as well as trophoblast immunomodulation participates in generating tolerance. There is alteration of both innate and adaptive immunity. Maternal immune tolerance varies with the gestation with early pregnancy requiring acceptance of fetus and later pregnancy precipitation of labor. Thus the immune response in pregnancy is complex and unique.

Maintaining immunological tolerance during pregnancy necessitates adjustments in the maternal immune system. These adaptations aim to sustain the pregnancy without compromising the mother's ability to combat infections. However, these changes also entail an increased susceptibility to certain infections. Furthermore, immune alterations can impact the course of inflammatory, autoimmune diseases, or coagulopathies, potentially leading to either improvement or worsening of these conditions.

- Hormonal changes lead to immunological changes for fetal tolerance
- Alteration in maternal immune system may lead to coagulopathies, alteration in autoimmune, inflammatory, and infective diseases

INNATE IMMUNITY

Complement

While there is an increase in cleaved complement proteins (C3a, C4a, C5a, C4d, C3a, C3, C9, and C5b9), complement inhibitors also see a rise **(Fig. 3)**. Notably, the elevation of C3 and C5 is minimal in the first trimester but becomes significant in subsequent trimesters. Complement proteins play crucial roles in placentation, maintaining vascular integrity, and regulating adaptive immunity. However, an imbalance in these proteins may lead to complications such as preeclampsia.

Pregnancy induces a hypercoagulable state, with fibrinogen and factor VII levels increased fourfold compared to the nonpregnant state. Additionally, elevated acute-phase reactants, complement, and coagulation proteins synergistically heighten the risk of deep vein thrombosis.

Granulocytes

Neutrophilic alterations lead to change in the number, function, or activity of neutrophils. They start increasing by 13 weeks of gestation, keep on increasing till second and remain more than nonpregnant till delivery **(Fig. 2)**. Some studies show that there is impaired neutrophil chemotaxis and phagocytosis.

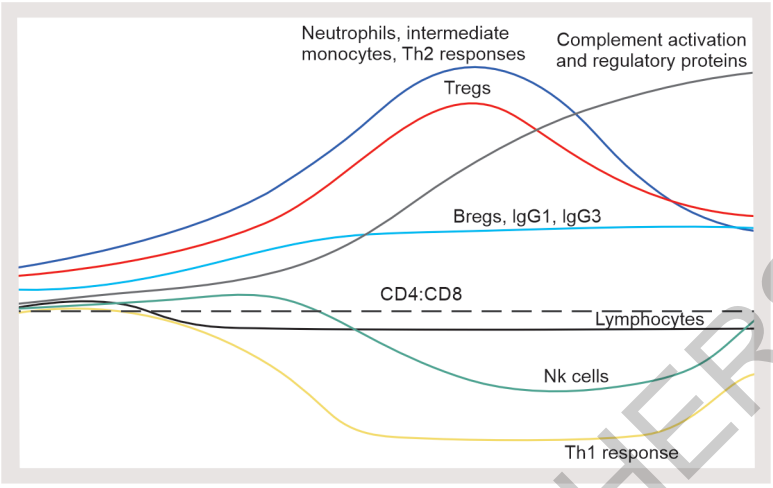

FIG. 3: Variation of immune cells in different trimesters.

While neutrophils are essential for host defense against infections, excessive neutrophil activation and inflammation can be detrimental.

Monocytes

Monocytes, while remaining fairly constant in terms of number, experience significant changes in their activation profile in pregnancy. Monocytes can be classified into different subpopulations based on the expression of cell surface markers. The three main subsets are classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and nonclassical ($CD14^{+}CD16^{++}$) monocytes. While classical monocytes have mainly phagocytic action, nonclassical have inflammatory activity. It is the intermediate monocytes which are increased in pregnancy **(Fig. 2)**. Intermediate monocytes are responsible for antigen presentation and inflammation.

Major adaptation is a shift in cytokine production toward an anti-inflammatory profile, with increased levels of cytokines like interleukin-10 (IL-10), which help prevent an immune attack on the fetus **(Fig. 4)**. Additionally, the phagocytic activity of monocytes is enhanced, allowing them to more effectively clear apoptotic cells and pathogens, thus reducing the risk of infections that could jeopardize the pregnancy. Furthermore, monocytes modulate their antigen presentation capabilities, promoting immune tolerance to fetal antigens and facilitating a harmonious maternal-fetal relationship.

Natural Killer Cells

During the first trimester of pregnancy, there is heightened natural killer (NK) cell activity. Mature NK cells increase in the peripheral blood, while immature NK cells become more prevalent in the decidua. Decidual NK cells play a crucial role in maintaining immune tolerance at the maternal-fetal interface, promoting

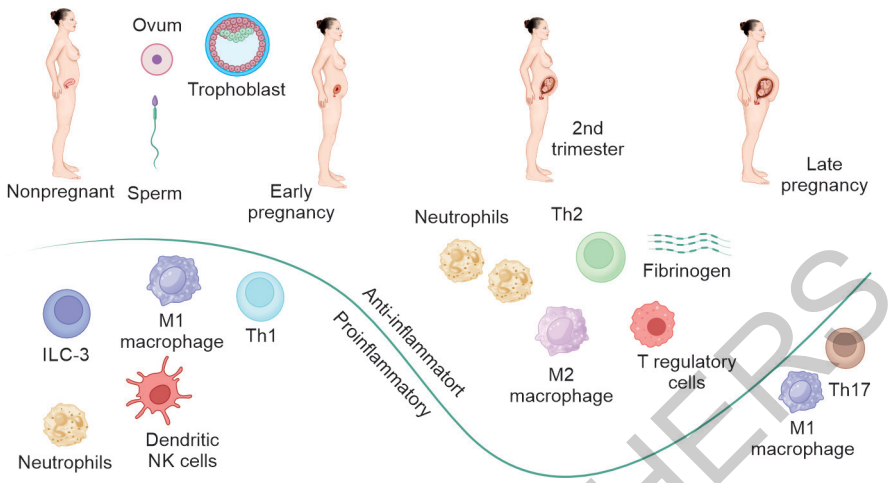

FIG. 4: Cellular changes during different trimesters of pregnancy shifting TH1 to TH2 immunity. (ILC-3: innate lymphoid cell type 3; NK: natural killer; Th1: type 1 T helper; Th2: type 2 T helper; Th17: type 17 T helper)

trophoblast invasion, and remodeling spiral arteries. Mature NK cells are more cytotoxic, facilitating antibody-dependent cellular cytotoxicity, whereas immature NK cells enhance the production of interferon-γ (IFN-γ), tumor necrosis factor-β (TNF-β), IL-10, IL-13, and granulocyte–macrophage colony-stimulating factor (GM-CSF), which contributes to antipathogen defense.

As pregnancy progresses into the second trimester, NK cell activity gradually decreases **(Fig. 2)**. This reduction is influenced by the increased expression of trophoblastic human leukocyte antigen (HLA)-G, HLA-E, and HLA-C, which further dampen NK cell activity. By downregulating NK cell activity, the maternal immune system fosters a state of immune tolerance toward the fetus and shifts toward a more anti-inflammatory state. During this period, the number of NK cells decreases, and their phenotype changes to a less cytotoxic type. The production of anti-inflammatory cytokines, especially IL-10 and transforming growth factor-β (TGF-β), increases. NK cells also interact with regulatory T cells (Tregs) and dendritic cells to maintain immune balance.

Alteration in innate immunity comprises of:

- Increase in cleaved components of complement and complement inhibitory proteins
- Hypercoagulable state
- Increased number and function of neutrophils
- Conversion of M1 predominant macrophages to M2 type
- Decrease in NK cell to a conversion to a less cytotoxic type
- Modulation of toll-like receptor (TLR) signaling to prevent excessive inflammation and fetal harm

ADAPTIVE IMMUNITY

T Cells

There is a decrease in absolute lymphocyte count during pregnancy, especially affecting T helper (Th) 17 cells and cytotoxic T cells **(Figs. 2 and 3)**.

B Cells

B cells decrease in pregnancy due to suppression of B cell lymphopoiesis and deletion of autoreactive B cells. This decrease persists till 1 month postpartum. B cell in pregnancy can be protective or harmful. Protective B cell produces asymmetric antibodies that bind to paternal antigens but do not destroy them. Harmful autoantibodies, e.g., antiphospholipid antibodies may terminate pregnancy.

Immunoglobulins

Immunoglobulin G1 (IgG1) and IgG3 levels are higher in pregnancy compared to nonpregnant women. IgG1 can cross placenta, providing protection against infections for both the mother and the fetus. However, there is an overall decrease in total Ig during pregnancy. Depression of cell-mediated immunity, loss of protein in urine, hemodilution, transfer of IgG from mother to fetus across the placenta, or pregnancy-associated hormones, especially steroid hormones (decreasing protein synthesis) may be various reasons for decreased total Ig.

T Regulatory Cells

The second trimester is characterized by a significant peak in Treg levels followed by a decline **(Fig. 2)**. Tregs are increased in maternal circulation as well as decidua. They produce anti-inflammatory cytokines such as IL-10 and TGF-β, which help to suppress immune activation and inflammation. They express molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), which interact with their ligands on effector T cells and dendritic cells to suppress immune responses.

B Regulatory Cells

A type of B regulatory cell (Breg) increase during pregnancy ($CD19^{+}CD24^{hi}CD27^{+}$) while IL-10 producing ones decrease in third trimester.

Th1 to Th2 Shift

There is conversion of Th1 dominance to Th2 cell type. Th2 cells secrete anti-inflammatory cytokines including IL-4, IL-5, IL-10, and IL-13 are produced more during pregnancy. These cytokines promote B cell activation, antibody production, and suppression of inflammatory responses. Th1 cytokines such as

IFN-γ, IL-2, and TNF-α are downregulated to reduce proinflammatory responses that could harm the fetus. While Th2 responses are effective against extracellular pathogens, they are less effective against intracellular pathogens (e.g., viruses and some bacteria). Pregnant women may be more susceptible to infections by intracellular pathogens due to the Th1 suppression. Listeria monocytogenes, Toxoplasma gondii, and leprosy, malaria are more severe and there is increased mortality rates due to influenza and varicella.

Impact on adaptive immunity:
- Expansion of Tregs and Bregs
- Alterations in antibody production
- Shift toward a Th2-type cytokine profile
- Expression of immune checkpoint molecules (e.g., PD-1, CTLA-4) to dampen immune activation

Other Immune Modulators

Indoleamine 2,3-dioxygenase (IDO), an enzyme responsible for the breakdown of tryptophan, is produced by both trophoblast cells and macrophages. This enzyme is crucial in inhibiting the activation of decidual α/β T cells. Additionally, the expression of IDO may be regulated by cytotoxic T lymphocyte antigen 4 (CTLA4), a protein expressed by Tregs. Overall pregnancy shows accelerated anti-inflammatory response with suppression of proinflammatory changes **(Table 1)**.

Trophoblast immunomodulation:
- Expression of immune-inhibitory molecules (e.g., HLA-G, PD-L1)
- Production of factors like IDO, which suppresses T cell activation

Impact of gestational age: Maternal immune adaptations vary throughout pregnancy, with distinct changes occurring during different trimesters:
- Early pregnancy—immune tolerance mechanisms to establish fetal-maternal tolerance
- Later stages of pregnancy involve a resurgence of immune activity to prepare for labor and delivery

TABLE 1: Other immune modulators in pregnancy.

Increased anti-inflammatory response	Decreased proinflammatory response
IL-4, 5, 10	IL-12,2
• TGF-beta • PIBF	• TNF-alpha • NK cells • Classical monocytes
• Intermediate monocytes • T regulatory cells • Th2	Th17Th1

(IL: interleukin; NK: natural killer; PIBF: progesterone-induced blocking factor; TGF-beta: transforming growth factor-beta; Th: T helper; TNF-alpha: tumor necrosis factor-alpha)

IMMUNO-HORMONAL INTERACTION

Hormonal fluctuations have a significant impact on the differentiation of Th cells. While lower levels of estradiol favor Th1 response the surge in this hormone during pregnancy promotes Th2 differentiation. Estrogen receptors (ERs) are present on lymphocytes, macrophages, and dendritic cells. Estrogen receptor α are present more on lymphocytes and Erβ on B cells. Estrogen also causes expansion of Treg and suppression of surface markers and secretion of granzyme and Fas ligand (FasL) on NK cell.

- Hormone receptors are present on immune cells
- Effect of estrogen on immunity is determined by its concentration
- Progesterone induces an anti-inflammatory response
- Progesterone increases the risk of genitourinary infections and that of acquiring HIV infection

Progesterone receptors are found on epithelial cells and various other immune cells such as mast cells, eosinophils, macrophages, dendritic cells, and lymphocytes. Progesterone can also bind to glucocorticoid receptor. Progesterone in pregnancy inhibit Th1 cytokine production and favor those of Th2. It also dampens TLR-induced cytokine production, innate immune responses, and the production of nitrite, nitric oxide, and TNF-α, resulting in an overall anti-inflammatory response in maternal circulation. However, progesterone also alters genital mucosal immune responses, potentially increasing the risk of acquiring HIV infection during pregnancy. Furthermore, progesterone and progesterone-induced blocking factor (PIBF) directly stimulate the production of IL-10, further contributing to immune modulation during pregnancy.

SUGGESTED READINGS

1. Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal Immunological Adaptation during Normal Pregnancy. Front Immunol. 2020;11:575197.
2. Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. Horm Behav. 2012;62:263-71.
3. De la Morena MT. Immunologic Changes During Pregnancy. In Stiehm's Immune Deficiencies; Elsevier Inc.: Amsterdam, The Netherladns; 2014. pp. 815-22.

PREGNANCY AND SKIN

Salient Features

- **In-depth coverage:** A detailed textbook on pregnancy-related dermatoses, incorporating the latest advances in the pathogenesis of various disorders
- **Reader-friendly format:** Designed with clinical photographs, illustrations, bullet points, and flowcharts for easy understanding and quick reference
- **Therapeutic safety:** Includes a dedicated chapter on the safety of therapeutic strategies for treating cutaneous diseases during pregnancy
- **Quick reference guide:** A concise resource tailored for physicians, gynecologists, and dermatologists
- **Interdisciplinary approach:** Bridges dermatology and obstetrics with insights for holistic care of pregnant patients with skin conditions
- **Comprehensive yet concise:** Balances detailed explanations with brevity, making it an ideal resource for both in-depth study and quick reference

Sanjeev Gupta MD DNB MNAMS is working as Professor and Head, Department of Dermatology, MM Institute of Medical Sciences and Research MMDU, Mullana, Ambala, Haryana, India. He is a member of most of national and international academic societies. He has around 170 publications, 4 books and 17 book chapters to his credit. He has invented many dermatological techniques and instruments to simplify the procedures and reduce the cost. Twenty-six of such inventions have been published one of the most prestigious journals of dermatology—Journal of the American Academy of Dermatology USA. He was awarded with "Making a Difference" award by the American Academy of Dermatology, USA. He is the first Indian to be honoured with this prestigious award. He has served his professional association [Indian Association of Dermatologists, Venereologists, and Leprologists (IADVL)] as Executive Committee Member at the state level as Treasurer, Secretary, Vice President, and President and also at the National level as Joint Secretary and Vice President IADVL. He was honoured with the LN Sinha Award by IADVL in 2013 and the ACSI Innovation Award 2021 by the Association of Cutaneous Surgeons of India (ACSI). He is the recipient of the Dr BM Ambady Oration awarded at DERMACON 2025 Jaipur.

Rohit Batra MD is a renowned Dermatologist associated with Sir Ganga Ram Hospital, Delhi, and is Head and Founder of Dermaworld Skin and Hair Clinics, New Delhi, India. His areas of interest are clinical dermatology, pediatric dermatology, aesthetic dermatology, trichology and multidisciplinary care of dermatological disorders. He has numerous presentations at various national and international conferences. He has been the architect of two of the most famous Dermatology Conclaves—Dermatology and Allied Specialities Summit (DAAS) and Acne India Summit. A prominent organizational guru and a mentor for many, he has held various roles and posts in the IADVL including the President of the IADVL- Delhi State Branch.

Mudita Gupta MD is currently working as Associate Professor, Dermatology Department, Indira Gandhi Medical College and Hospital, Shimla, Himachal Pradesh, India. In addition to clinical practice, she is a prolific researcher in the field of dermatology, with innumerable publications in various prestigious journals. She has given many presentations at various national conferences and authored chapters in dermatology textbooks. Her research mainly focuses on sexually transmitted diseases, immunobullous disorder, and pediatric dermatology and has contributed to advancements in both diagnostic techniques and treatment strategies.

Printed in India

Available at all medical bookstores or buy online at www.ejaypee.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road, Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers
Follow us on instagram.com/JaypeeMedicalPublishers

Shelving Recommendation
DERMATOLOGY

ISBN 978-93-6616-500-4