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The Impact of Sex Hormones on the Periodontium during Woman's Pregnancy

A graduation research project is submitted to Collage of Dentistry , University of Misan as partial fulfilments of the Requirements for Bachelor's degree in Dentistry

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

عَلَّمَ الْإِنسَٰنَ مَا لَمْ يَعْلَمْ

سورة العلق (الآية ٥)

صَدَقَ اللّٰهُ العَلِيُّ العَظيم

Dedication

To everyone who gave us support in all forms , love, and the kind words, to everyone who was a partner with us in this trip and opened and facilitated for us to reach one of our goals, to everyone who taught us even a letter.

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I would like to express my deep appreciation and indebtedness particularly to my supervisor **Dr.Ibtisam Kareem** for her invaluable guidance and experience.

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I'm proud to be one of her students. All family and friends and others who in one way or another shared their support , thank you GOD bless you all.

Certification

I certify that this project entitled:

The impact of sex hormones on periodontium during women's pregnancy

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Abstract

The two main female Sex hormones are estrogen and progesterone ,types of estrogens are E1, E2, E3, E4 and the most potent one is E2 (Estradiol), progesterone and Estradiol are called female Sex steroid, pregnancy is characterized by hormonal changes, these changes are regulated by fluctuations in hormones such as Progesterone, Testosterone, Androstenedione, Dehydroepiandrosterone,Estradiol, Prolactin, human Placental Lactogen, human Chorionic Gonadotropin,and Thyroid hormones, which promote the mother's development and the fetus(maternal-fetal development), These changes can lead to many effects on periodontium like gingivitis without plaque changed, pyogenic granuloma, increased bone resorption, decrease keratinization and vascular dilatation, alert rate and pattern of collagen production in gingival tissue which reduce the repair ability in these tissues.

Aims of review:

To focus on the essential hormones during the pregnancy and the changes that occur to them & To know the effects of these changes on the periodontium and increase awareness in pregnant women in this regard.

Conclusion:

pyogenic granuloma, increased bone resorption, increased the amount of gingival inflammation - with minimal or no plaque are the most common effects of hormonal changes during pregnancy.

Key words

Estradiol, progesterone, hormonal changes, gingival inflammation, pyogenic granuloma

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List of Abbreviations

abbreviations	Meaning
FSH	Follicle Stimulating Hormone
PROG	Progestrone
NK	Natural Killers
LDL	Low Density Lipoprotein
HDL	High Density Lipoprotein
(DC)	Dendritic Cells
ECM	Extracellularmatrix
(PD)	Parkinson Disease
(ER)	Estrogen Receptor
HCG	Human Chorionic Gonadotropin
βHCG	Bhuman Chorionic Gonadotropin
FSH	Follical Stimulating Hormone
LH	Luteinizing Hormone
AFP	Alpha Fetoprotein
PAPP_A	Pregnancy Associated Plasma Protein
DHEA	Dehydroepiandrosterone
Dhea-Sulfate	Dehydroepiandrosterone Sulfate
16_ OH DHEA Sulfate	16 Hydroxy Dehydroepiandrosterone Sulfate
HPL	Human Placental Lactogen
GnRH	Gonadotropin Releasing Hormone
MMP	Matrix Metalloproteinases
MPFU	Maternal Placentally-Produced Factors
T	Testosterone
P4	Progesterone
A4	Androstenedione
SLC	Small Luteal Cell
DHT	Dihydrotestosterone
CRH	Corticotropine Releasing Hormone
11_β_HSD	11-β-Hydroxysteroid- Dehydrogenase
GC	Glucocorticoids
HPA	Hypothalamic Pituitary Adrenal Axis
GI	Gingival Index
PI	Plaque Index
BOp	Bleeding On Probing
PPD	Periodontal Pocket Depth
COC	Combined Oral Contraseptive
PG	Pyogenic Granuloma
TNF	Tumor Necrosis Factor
CCL2	Chemokine Ligand 2
IL	Interleukin
LPS	Lipopolysaccharide
ROS	Reactive Oxygen Species
PMNS	Polymorphonuclear Leukocytes
BFGF	Basic Fibroblast Growth Factor
VEGF	Vascular EndothelialGrowth Factor

Ang	Angiopoietin

Chapter One

Chapter One : Introduction

Hormones are traditionally defined as chemical signals, transported to their target tissues in the blood; today, however, that definition is often expanded to include all chemical messengers that bind to target cells with high affinity. So far, more than 100 hormones have been identified in the human body, and this rises to more than 200 if hormone-like substances are included (Bit.ly/PFHormones; Silver and Kriegsfeld, 2001).

They can be broadly divided into three major classes , peptide hormones steroid hormones,amino acid-derived hormones(Foster et al, 2019).

Steroid hormones are lipids, they rapidly diffuse across the phospholipid bilayer of their target cell membranes and exert their effects by binding to receptors in the cytoplasm or nucleus (Ozawa, 2006). Steroid hormones tend to precipitate their desired effects by modulating the activity of particular genes in cells(Kleineand Rossmanith,2016).

Estrogens are the primary female sex hormones and belong to the steroid hormone family. Although estrogens are primarily thought of as female hormones, they exert a broad spectrum of functions in both males and females (Hess RA, Cooke PS. 2018).There are in total four different types of endogenous estrogens, namely estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4)(Cui J, Shen Y, Li R. 2013).

Progesterone (PROG) was one of the first hormones to be identified, and together with estradiol, it is generally known as a female sex steroid(Sundstrom-Poromaa,I .et al. 2020).

Pregnancy is characterized by hormonal changes, critical for the mother's physiological adaptation, exercising a role in the fetus's development, maintenance, protection, and nutrition. Since born, the neuroendocrine system's involvement is necessary to prevent the embryo from being rejected by the mother's immune system. These changes are regulated by fluctuations in hormones such as Progesterone, Testosterone, Androstenedione, Dehydroepiandrosterone, Estradiol, Prolactin, human Placental Lactogen, human Chorionic Gonadotropin, and Thyroid hormones, which promote the mother's development and the fetus (maternal-fetal development). Therefore, given the great importance of these hormones during pregnancy(Voltolini C, Petraglia F.2014).

Periodontium is a unique structure composed of two fibrous (gingival and periodontal ligament) and two mineralized (cementum and alveolar bone) tissues [B.L mealey and et al 2003].Recent cross-sectional and longitudinal studies have further confirmed and extended the association between pregnancy and gingival condition in many cultural and ethnic groups(a tilakaratne and et al 2000).

Pregnancy probably has an effect only on the gingiva and has no permanent effects on periodontal attachment, meantime, the effect of female sex hormones on periodontal ligament and tooth supporting alveolar bone has rarely been investigated [P.mishra and et al 2013]

Aims Of Review

1) To focus on the essential hormones during the pregnancy and the changes that occur to them.

2) To know the effects of these changes on the periodontium and increase awareness in pregnant women in this regard.

3) To emphasize the importance of oral hygiene care and its role in reducing or controlling these effects.

Chapter

Two

Chapter two :General view of sex hormones

2.1 Endocrine system

The endocrine system is a series of glands and tissues that produce and secrete hormones, which are used by the body to regulate and coordinate vital bodily functions, including growth and development, metabolism, sexual function and reproduction, sleep and mood. The endocrine system is incredibly complex: it consists of dedicated, specialized endocrine glands – such as the thyroid, parathyroid and adrenal glands – together with tissues such as fat (adipose tissue) and bone that have a secondary endocrine function and also secrete a range of hormones (Ganapathy MK, Tadi P. 2020).

2.2 Endocrine and exocrine glands

All glandular tissues produce secretions. Most glandular structures are epithelial in origin, and many are folded and organised into recognisable glands with a central duct. Glands possessing a duct are exocrine glands the duct acts as a conduit into which secretions are released before being carried away to their sites of action. Exocrine glands include many of the digestive glands in the gut, sweat glands in the skin and mucus-producing glands in the mucous membranes of the mouth and reproductive tracts. In contrast, endocrine glands have no duct, but release their secretions, called hormones, directly into the blood . For this reason, most endocrine glands are highly vascularised, and many of their component cells are in direct contact with blood capillaries. This close association with blood vessels facilitates the direct release of hormones into the blood and glands. As an example of this, adrenocorticotropic hormone regulates the release of the long-term stress hormone, cortisol, from the adrenal cortex. As the pituitary gland regulates hormone release from other endocrine glands, it is often referred to as the ‘master’ gland. This is something of a misnomer as the release of stimulating hormones from the pituitary gland is, itself, under the control of hormones produced by the hypothalamus (Knight J et al. 2020).

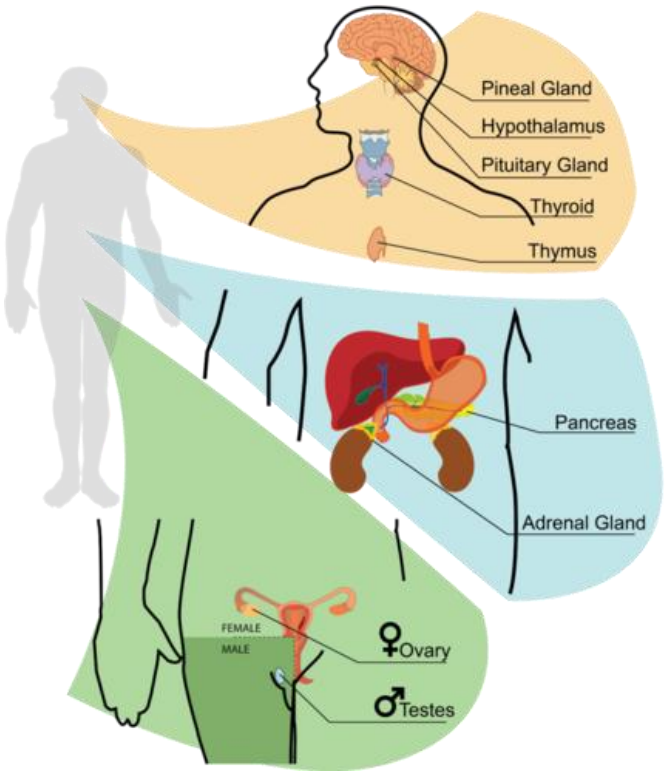


Fig (1) : the position of the major endocrine glands in the body

(Aptekar,R. 2025*)*.

2.3 Hormones

Hormones are traditionally defined as chemical signals, transported to their target tissues in the blood; today, however, that definition is often expanded to include all chemical messengers that bind to target cells with high affinity. So far, more than 100 hormones have been identified in the human body, and this rises to more than 200 if hormone-like substances are included (Bit.ly/PFHormones; Silver and Kriegsfeld, 2001). Hormones exert their physiological effects by binding to specific receptors associated with their target cells. Many drugs have been designed to targe these receptor sites, either to mimic the actions of hormones (for example, in the case of a hormone deficiency such as hypothyroidism, which is treated with levothyroxine) or to act as competitive antagonists

to physically block the receptor, preventing the natural hormone from binding and exerting its effect. Hormones can be broadly divided into three major classes:

- Peptide hormones.
- Steroid hormones.
- Amino acid-derived hormones(Foster et al, 2019).

2.4 Steroid hormones

Steroid hormones are lipids (fats), mostly derived directly from cholesterol, which acts as a precursor molecule for steroid biosynthesis. Examples include:

- estrogen;
- Progesterone;
- Testosterone;
- Cortisol.

As steroid hormones are lipids, they rapidly diffuse across the phospholipid bilayer of their target cell membranes and exert their effects by binding to receptors in the cytoplasm or nucleus (Ozawa, 2006). Steroid hormones tend to precipitate their desired effects by modulating the activity of particular genes in cells(Kleine and Rossmanith,2016).

2.4 Female Sex Hormone

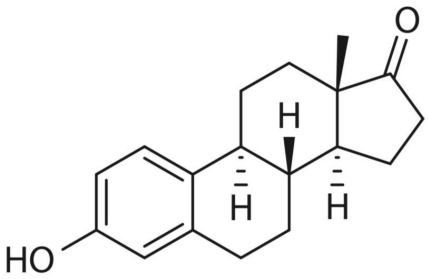
2.4.1 Estrogen :

Estrogens are the primary female sex hormones and belong to the steroid hormone family. Although estrogens are primarily thought of as female hormones, they exert a broad spectrum of functions in both males and females. Sex organ development and the regulation of reproduction in females are part of the main effects of estrogens, but they also have effects on the brain, bone , metabolism, cardiovascular system, and immune system. In females, estrogens take part in the regulation of the menstrual cycle and are responsible for both primary and secondary sexual .Similarly, estrogens play an equally

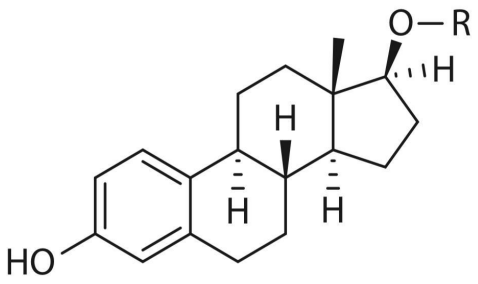
important role in for example sperm maturation and erectile function in males (Hess RA, Cooke PS 2018).

There are in total four different types of endogenous estrogens, namely estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). As the most potent type of estrogen, E2 is produced in the ovary and is the predominant estrogen in premenopausal females(Cui J, Shen Y, Li R)(2013).

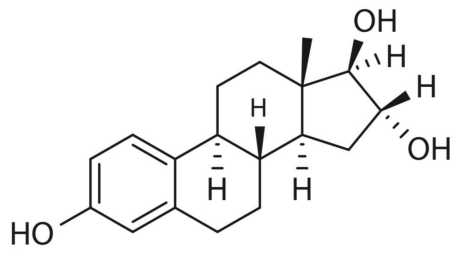
E1 is an estrogen primarily produced by extragonadal tissues (such as adipose tissue with similar levels in pre- and postmenopausal females and males. E1 can be reversibly transformed to E2 in peripheral tissues E3 and E4 are predominantly produced during pregnancy, where E3 is produced by the placenta and E4 by the fetal liver (Cui J, Shen Y, Li R. 2013).



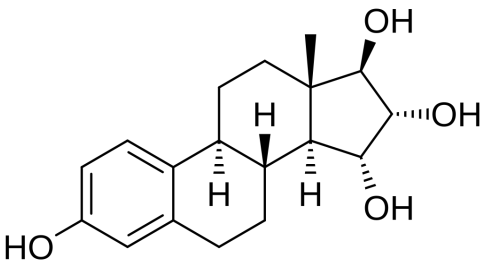
Estrone (E1) (Thomas P, Pang Y, Filardo EJ, Dong J.)(2005)



Estradiol (E2) (Thomas P, Pang Y, Filardo EJ, Dong J.)(2005)



Estriol (E3) (Chourasia TK, Pang Y, Thomas P.)(2015)



Estetrol (E4) (Holinka CF.2008)

Fig(2) Estrogen stracture

2.4.2 Estrogen synthesis :

The anterior pituitary gland, at the time of puberty, begins secreting gonadotropins: follicle-stimulating hormones and the luteinizing hormone, which act on the ovaries to begin cyclical production and secretion of the two main female sex hormones: estrogen and progesterone (Amar S, Chung KM. 2000).The primary site for estrogen synthesis is the ovary in pre-menopausal females. Here, E2 is produced by theca and granulosa cells that enable the conversion of cholesterol to E2 in a cooperative effort, illustrated in Figure 2 . Pregnenolone is the precursor of all steroid hormones. After being produced in the mitochondria, pregnenolone is transported to the endoplasmic reticulum where the remaining steps in estrogen synthesis take place .. While the initial steps of steroidogenesis largely take place in theca cells, granulosa cells themselves can produce

progesterone from cholesterol.Testosterone in females is produced in the granulosa cells.E2 synthesis in granulosa cells is regulated by FSH. (Melchinger P, Garcia BM 2023) In males, E2 is produced in the testis, by a similar process between Sertoli and Leydig cells(Cui J, Shen Y, Li R. 2013).

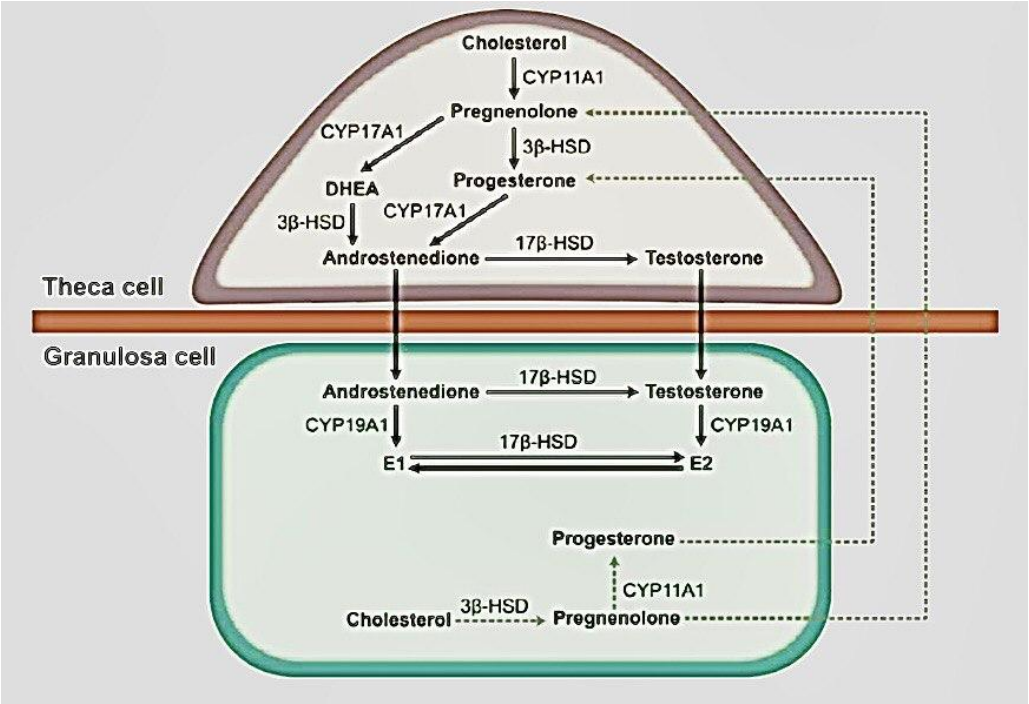


Fig (3) :Synthesis of estradiol (E2) by granulosa and theca cells in the ovarian follicle(Christenson L.2000).

2.4.3 Physiological Actions of Estrogen

In general, ovarian steroid hormones (estrogen and progestrone) function in a coordinated fashion to support reproductive activity of the female including development of the ovum, development and maintenance of the corpus luteum to sustain a fertilized ovum, maintenance of pregnancy, and preparation of the breasts for lactation.Usually, estrogen and progesterone complement or enhance each other's actions in the female

reproductive tract. Occasionally, they antagonize or modulate each other's actions (Costanzo,L,S.2018).

Estrogen causes the appearance of secondary sex characteristics in the young woman. Such changes include the following:

- Enlargement of the accessory organs of the female reproductive system (uterine tubes, uterus, vagina, external genitals)
- Development of the breasts.
- Increased deposits of fat beneath the skin in general, and particularly in the hips and breasts.
- Widening and lightening of the pelvis
- Onset of menses, or the menstrual cycle.
- Estrogen also has metabolic effects. For example, it helps maintain low total blood cholesterol levels (and a high HDL level) and facilitates calcium ion uptake, which sustains bone density(Marieb,E,N;Keller,S,M.2022).
- Maturation and maintenance of uterus, fallopian tubes, cervix, and vagina.
- Responsible for proliferation and development of

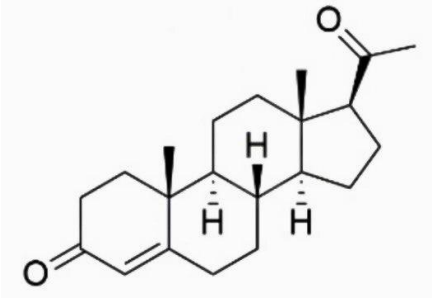
ovarian granulosa cells.

- Lowering uterine threshold to contractile stimuli
- Stimulation of prolactin secretion.
- Decrease LDL cholestrol
- Anti-osteoporosis (Costanzo,L,S. 2018).

2.4.4 Progesterone

Progesterone (PROG) was one of the first hormones to be identified, and together with estradiol, it is generally known as a female sex steroid. PROG is an endogenous 21-carbon steroid hormone synthesized from cholesterol by way of pregnenolone and is a major gonadal hormone synthetized in the corpus luteum of the ovaries and also by the placenta during pregnancy. To a lesser extent, PROG is also produced at much lower levels by the adrenal cortex, Leydig cells of the testes in men, adipose and other tissues. As with some other steroids, PROG is also synthesized by the nervous system by neurons and glia and also acts on nervous system tissues. All enzymes necessary for the

conversion of cholesterol to pregnenolone and subsequently to PROG are also widely distributed within the brain (Sundstrom-Poromaa,I .et al.2020).



Fig(4) **Progestrone** (Hill, M. et al.2007).

2.4.5 Physiological Actions of Progesterone

Progesterone is primarily known as the pregnancy hormone in females, and most of its function relates to maintaining pregnancy specifically by:

- Decreased pain sensitivity -pregnancy-induced analgesia(Frolich, M.A.2016)
- The endometrial glands become tortuous and contain fluid containing glycogen, glycoproteins and glycolipids which provide nutrition to blastula if fertilization occurs.
- The stroma of endometrium becomes oedematous. Thus, progesterone is responsible for secretory phase of the endometrial cycle and prepares the endometrium to receive the zygote(Khuran i. 2015)
- progesterone is known to be essential for implantation (K.I. Black et al. 2017).
- Progesterone decreases the uterine motility.
- Inhibition of lactation during pregnancy.
- Plays a role in the menstrual cycle causing capillary growth and development with the result of increased vascularization and blood flow.
- In males, progesterone functions to facilitate spermiogenesis and androgen synthesis.

- Progesterone is known as a thermogenic steroid which increases the basal body temperature by 0.5°C in the postovulatory phase(Khuran i. 2015).
- Progesterone is estradiol's partner hormone in bone. P4 appears to play important roles in achievement of an ideal peak bone mineral density (BMD Prior, J. C 2018).
- Progesterone alters the secretion and release of various neurotransmitters in the hypothalamus and other areas of the brain and thereby decreases the appetite and produces somnolence..
- Progesterone decreases the serum HDL(Chappell CA,et al.).
- progesterone functions as vasodilator , thus contributing to reducing blood pressure during pregnancy (Ngene and Moodley, 2019).
- Progesterone acts as an immunomodulator that interacts with the immune system and exerts anti-inflammatory effects throughout pregnancy, inhibits the activity of dendritic cells (DCs) that generate proinflammatory responses,controls the activity of natural killer (NK) cells and the differentiation of T cells into T-helper cell type 2 (Th2)(Szekeres-Bartho J. 2009).

2.5 Abnormalities in hormones secretion

2.5.1 Decreased estrogen levels (Hpoestrogenism):

- in middle-aged women lower levels of female sex hormone were associated with higher risk of suffering from OSA symptoms(Wang H. 2022).
- The last step of the wound healing is the remodeling phase, which relies on a controlled balance between the synthesis and degradation of the ECM, and estrogen.(Billon R. etal.2017).
- in addition to genetic and environmental (particularly stress) factors, we include sex-hormone status in women. By interacting with genetic make-up and stress expo sure history, fluctuating hormones in women are able to affect brain structure andfunction and contribute to, at least in part, symptom atology of anxiety and depression that more frequently affects women.(Wang H. et.al 2022).
- Estradiol decline with increasing age in both men and women and likely
- contribute to bone loss and fracture(Jane A. C.2015).

- Autoimmunity (Bakalov VK, etal 2002).
- the skin undergoes conspicuous decline in appearance and function. This is especially true in exposed areas (face, neck, and hands) and carries messages of age-related decline (Edwin D. L. , Naftoli F. 2021).
- neuroprotective effects in stroke,Parkinson disease (PD), and Alzheimer diseas e (AD),so when it decreases the risk of developing this conditions increases(Shearman, A.M., et al.2005).
- The incidence of cardiovascular diseases is low in premenopausal women but increases substantially after menopause (matching that seen in men), suggesting that estrogens protect the female cardiovascular system.(Farquhar, C.M.)(2005).
- the skin undergoes conspicuous decline in appearance and function. This is especially true in exposed areas (face, neck, and hands) and carries messages of age-related decline (Edwin D. L., Naftolin F.)(2021).
- lower fertility or even infertility(Nelson LM,)(2001).

2.5.2 Increased estrogen levels (Hyperestrogenism)

- enlargement of the uterus and breasts IN FEMALE Lavin N. 2012
- One out of five men seeking first medical help for erectile dysfunction had elevated serum estradiol values. Significant health comorbidities, orgasmic function impairment, and more severe erectile dysfunction were all linked to hyperestrogenismBelladelliF.,2023
- postmenopausal breast cancer risk was increased in women with higher estrogen levels,particularly with respect to tumors that were classified as both estrogen receptor (ER) Missmer SA. Etal 2004.especially obese women Margot P. C.,Michael E. G 2009
- . gynecomastia, feminizationLewis R. Goldfrank; Neal Flomenbaum 2006.
- hyperestrogenism is acknowledged as ordinary risk elements for the development of Enomaterial polyps Rom JM. E.2022

2.5.3 Decreased levels of Progestrone

- An inverse association was found between low levels of progesterone and clinical Rheumatoid arthritis(Mohammed M S.etal)(2025).
- Lower levels of progesterone in pregnancies leading to autismM. Whitaker-Azmitia etal.2014
- Low progesterone levels are a good predictor for miscarriageM.A. Osmanağaoğlu *et al.2010.*A single serum progesterone measurement taken in early pregnancy is valuable in the immediate diagnosis of early pregnancy failure and the long term prognosis of viability(Mohamed A. H.)(1995)
- pregnant women with preeclampsia have lower levels of progesterone, and treatment of gestational hypertension with a progesterone synthetic metabolite has been proven efficacious (Amaral et al.,)(2014).

2.5.4 Increased progestrone levels

It contributes in ciliarydysfunction and subsequently may be a possible cause ofectopic pregnanc(.Yoav Paltieli)(2000) , elevated levels of progesterone did not significantly affect fertilization rates(Vanni et al., 2017).

Chapter three

Chapter three: Hormonal Change during Pregnancy

Pregnancy is characterized by hormonal changes, critical for the mother's physiological adaptation, exercising a role in the fetus's development, maintenance, protection, and nutrition. Since born, the neuroendocrine system's involvement is necessary to prevent the embryo from being rejected by the mother's immune system. These changes are regulated by fluctuations in hormones such as Progesterone, Testosterone, Androstenedione, Dehydroepiandrosterone, Estradiol, Prolactin, human Placental Lactogen, human Chorionic Gonadotropin, and Thyroid hormones, which promote the mother's development and the fetus (maternal-fetal development). Therefore, given the great importance of these hormones during pregnancy, this chapter will explain the preclinical and clinical participation of sex hormones in maternal-fetal development. (Voltolini C, Petraglia F.2014).

3.1 Maternal Changes During Pregnancy

During a typical menstrual cycle, the corpus luteum degenerates about two weeks after ovulation. Consequently, concentrations of estrogens and progesterone decline rapidly, the uterine lining breaks down, and the endometrium sloughs off as menstrual flow. If this occurs following implantation, the embryo is lost in a spontaneous abortion. **The hormone hCG** normally helps prevent spontaneous abortion. It functions similarly to LH, and it maintains the corpus luteum, which continues secreting estrogens and progesterone. Thus, the uterine wall continues to grow and develop (fig. 4). At the same time, hCG inhibits the anterior pituitary gland's release of FSH and LH, halting the normal menstrual cycles. Detecting hCG in a woman's urine or blood is used to confirm pregnancy. The level of hCG in a pregnant woman's body fluids peaks at fifty to sixty days of gestation, then falls for the remainder of her pregnancy. Later on, measuring hCG has other uses. If a woman miscarries but her blood still shows hCG, fetal tissue may remain in her uterus, and this material must be removed. And other further tests, Chromosome Disorders, Prenatal Tests Detect Chromosome Abnormalities, are necessary for a definitive diagnosis. Secretion of hCG continues at a high level for about two months, then declines to a low level by the end of four months. Although the corpus luteum persists throughout pregnancy, its function as a source of hormones becomes less important after the first three months (first trimester), when the placenta secretes sufficient estrogens and progesterone . For the remainder of the pregnancy, placental estrogens and placental progesterone maintain the

uterine wall. The placenta also secretes a hormone called placental **lactogen** that, with the aid of placental **estrogens** and **progesterone**, stimulates breast development and prepares the mammary glands to secrete milk. Placental progesterone and a polypeptide hormone called **relaxin** from the corpus luteum and the placenta inhibit the smooth muscle in the myometrium, suppressing uterine contractions until the birth process begins. **Relaxin** action allows for greater movement at these joints, aiding passage of the fetus through the birth canal. Other hormonal changes during pregnancy include increased secretion of aldosterone from the adrenal cortex and of parathyroid hormone from the parathyroid glands. Aldosterone promotes renal reabsorption of sodium, leading to fluid retention. Parathyroid hormone helps to maintain a high concentration of maternal blood calcium, because fetal demand for calcium can cause hypocalcemia, which promotes cramps. Table 1 summarizes the hormonal changes of pregnancy. (Holes human anatomy & physiology Fifteenth edition, ,2018)

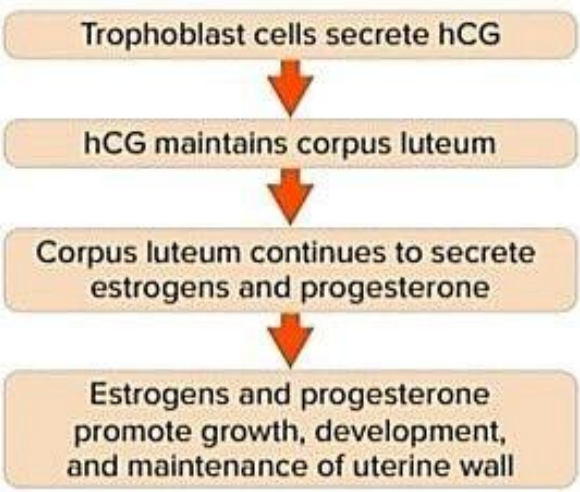


Fig 5 : Mechanism that preserves the utrine lining during early pregnancy((Holes human anatomy & physiology Fifteenth edition, ,2018)

|Table 1|Hormonal changes during pregnancy

1. Following implantation, cells of the trophoblast begin to secrete hCG.
2. hCG maintains the corpus luteum, which continues to secrete estrogens and progesterone.
3. As the placenta develops, it secretes abundant estrogens and progesterone.
4. Placental estrogens and progesterone a. stimulate the uterine lining to continue development. b. maintain the uterine lining. c. inhibit secretion of FSH and LH from the anterior pituitary gland. d. stimulate development of the mammary glands. e. inhibit uterine contractions (progesterone). f. enlarge the reproductive organs (estrogens).
5. Relaxin from the corpus luteum also inhibits uterine contractions and relaxes the pelvic ligaments.
6. The placenta secretes placental lactogen that stimulates breast development.
7. Aldosterone from the adrenal cortex promotes reabsorption of sodium.
8. Parathyroid hormone from the parathyroid glands helps maintain a high concentration of maternal blood calcium.

3.2 Birth Process

Pregnancy terminates with the birth process (parturition). **Progesterone** plays a major role in its start. During pregnancy, this hormone suppresses uterine contractions. As the placenta ages, progesterone concentration in the uterus declines, which stimulates synthesis of a prostaglandin that promotes uterine contractions. At the same time, the cervix begins to thin and then open. Changes in the cervix may begin a week or two before other signs of labor. Stretching of the uterine and vaginal tissues late in pregnancy also stimulates the birth process. This action initiates impulses to the hypothalamus, which in turn signals the posterior pituitary gland to release the hormone **oxytocin** , which stimulates powerful uterine contractions. Combined with

the greater excitability of the myometrium due to the decline in progesterone secretion, stimulation by oxytocin aids labor in its later stages.At the same time, dilation of the cervix reflexly stimulates an increased release of oxytocin from the posterior pituitary gland. As labor continues, positive feedback stimulates abdominal wall muscles to contract, helping to propel the fetus through the birth canal (cervix, vagina, and vulva) to the outside. Table 2 summarizes some of the factors promoting labor. Breastfeeding also contributes to returning the uterus to its original, prepregnancy size, because suckling by the new born stimulates the mother's posterior pituitary gland to release oxytocin. (Holes human anatomy & physiology Fifteenth edition,2018).

|Table 2| Factors contributing to the labor process

1. As the time of birth approaches, secretion of progesterone declines, and its inhibiting effect on uterine contractions lessens.
2. Decreasing progesterone concentration stimulates synthesis of prostaglandins, which initiate labor.
3. Stretching uterine tissues stimulates release of oxytocin from the posterior pituitary gland.
4. Oxytocin stimulates uterine contractions and aids labor in its later stages.
5. As the fetal head stretches the cervix, a positive feedback mechanism results in stronger and stronger uterine contractions and a greater release of oxytocin.
6. Positive feedback stimulates abdominal wall muscles to contract with greater and greater force.
7. The fetus is forced through the birth canal to the outside.

3.3 Milk Production and Secretion

During pregnancy, **placental estrogens** and **progesterone** stimulate further development of the mammary glands. Estrogens cause the ductile systems to grow and branch, and deposit abundant fat around them. Progesterone stimulates the development of the alveolar glands at the ends of the ducts. Placental **lactogen** also promotes these changes.Beginning about the fifth week of pregnancy, the anterior pituitary gland releases increasing amounts of **prolactin**. Prolactin is synthesized from early pregnancy throughout gestation, peaking at the time of birth. However milk secretion does not begin until after birth. This is because during pregnancy, placental progesterone inhibits milk production, and placental lactogen blocks the action of prolactin . Consequently, even though the mammary glands can secrete milk, none is produced. Following childbirth and the expulsion of the placenta, maternal blood concentrations of placental hormones rapidly decline. The action of prolactin is no longer inhibited. Prolactin stimulates the mammary glands to secrete milk. This hormonal effect does not occur until two or three days following birth. A reflex action controls this process and is elicited when the breast is suckled or the nipple or areola is otherwise mechanically stimulated. Then, impulses from sensory receptors in the breasts travel to the hypothalamus, which signals the posterior pituitary gland to release **oxytocin**. The oxytocin reaches the breasts by means of the blood and stimulates the myoepithelial cells in both breasts to contract (fig. 6). **prolactin** is released as long as breast feeding continues. However, if stimulation of the nipple does not occur regularly, the hypothalamus inhibits secretion of prolactin, and within about one week the mammary glands stop producing milk. To wean a nursing child, a woman may stop breastfeeding gradually, by eliminating one feeding per day each week. If a woman stops nursing abruptly, her breasts may become painfully engorged for several days. A woman who is breastfeeding usually does not ovulate for several months, because prolactin suppresses release of **gonadotropins** from the anterior pituitary gland. When a woman stops breastfeeding, the anterior pituitary gland stops secreting prolactin. Then FSH is released, and the menstrual cycle is activated. A new mother will be fertile approximately two weeks prior to the return of her menstrual period. Table 3 summarizes the hormonal control of milk production.(Holes human anatomy & physiology Fifteenth edition, 2018)

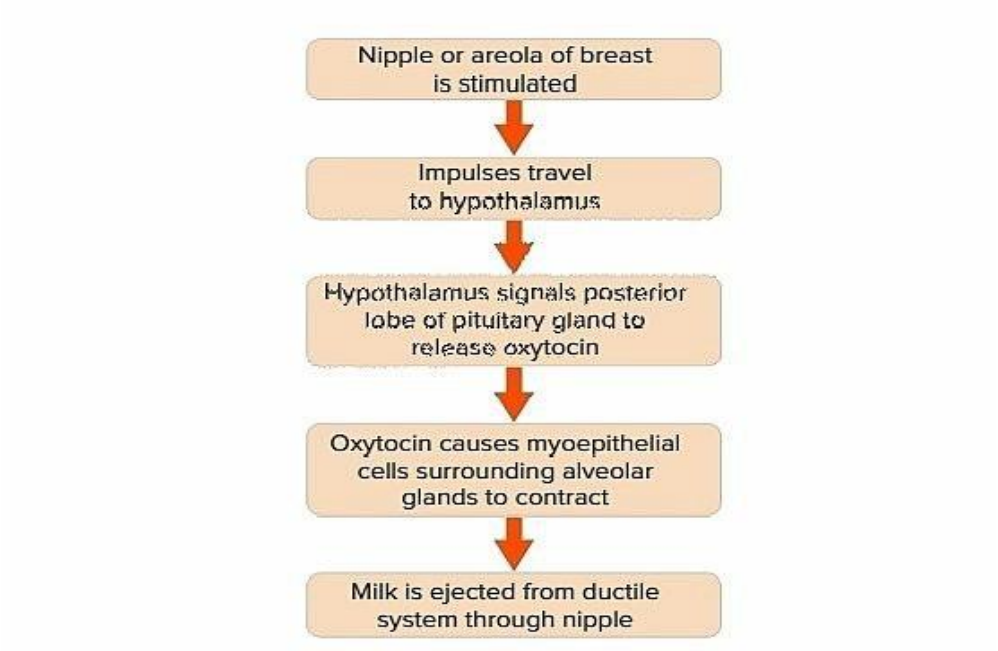


Fig 6 : Myoepthelial cells contract to release milk from alveolar gland(Holes human anatomy & physiology Fifteenth edition, ,2018)

|Table 3| Hormonal control of the mammary glands

Before Pregnancy (Beginning of Puberty)	Following Childbirth
Ovarian hormones secreted during reproductive cycles stimulate alveolar glands and ducts of mammary glands to develop.	1. Placental hormonal concentrations decline, so the action of prolactin is no longer inhibited.
During Pregnancy	2. The breasts begin producing milk.
1. Estrogens cause the ductile system to grow and branch.	3. Mechanical stimulation of the breasts releases oxytocin from the posterior pituitary gland.
2. Progesterone stimulates development of alveolar glands.	4. Oxytocin stimulates release of milk from ducts.
3. Placental lactogen promotes development of the breasts.	5. As long as breastfeeding continues, more prolactin is released; if the nipple is not stimulated regularly, milk production ceases.
4. Prolactin is secreted throughout pregnancy, but placental progesterone inhibits milk production and placental lactogen blocks the action of prolactin.	

3.4 Hormones of Pregnancy by trimesters

The duration of pregnancy is, by convention, counted from the date of the last menstrual period. Pregnancy lasts approximately 40 weeks from the onset of the last menstrual period, or 38 weeks from the date of the last ovulation. Pregnancy is divided into three trimesters, each of which

corresponds to approximately 13 weeks. Hormone levels during pregnancy are depicted in Figure 7.

♦ First trimester. **HCG** is produced by the trophoblast, beginning about 8 days after fertilization. As previously described, HCG "rescues" the corpus luteum from regression and, with an LH-like action, stimulates corpus luteal production of progesterone and estrogen. HCG levels are maximal at approximately gestational week 9 and then decline. Although HCG continues to be produced for the duration of pregnancy, its function beyond the first trimester is unclear.

♦ Second and third trimesters. During the second and third trimesters, the placenta, in concert with the mother and the fetus, assumes responsibility for production of steroid hormones. The pathways for the synthesis of progesterone and estrogen are shown in Figure 8**.** **Progesterone** is produced by the placenta as follows: Cholesterol enters the placenta from the maternal circulation. In the placenta, cholesterol is converted to pregnenolone, which then is converted to progesterone. **Estriol,** the major form of estrogen during pregnancy, is produced through a coordinated interplay of the mother and the placenta, and, importantly, requires the fetus. Again, cholesterol is supplied to the placenta from the maternal circulation and is converted to pregnenolone in the placenta. Pregnenolone then enters the fetal circulation and is converted to dehydroepiandrosterone-sulfate (DHEA sulfate) in the fetal adrenal cortex. DHEA-sulfate is hydroxylated to 16-OH DHEA-sulfate in the fetal liver. 16-OH DHEA-sulfate then crosses back to the placenta, where a sulfatase enzyme removes sulfate and aromatase converts it to estriol. The placenta also produces the peptide hormone **human placental lactogen (hPL)**, which is structurally related to growth hormone and prolactin (Physiology sixth edition By Linda .S. Costanzo, 2018).

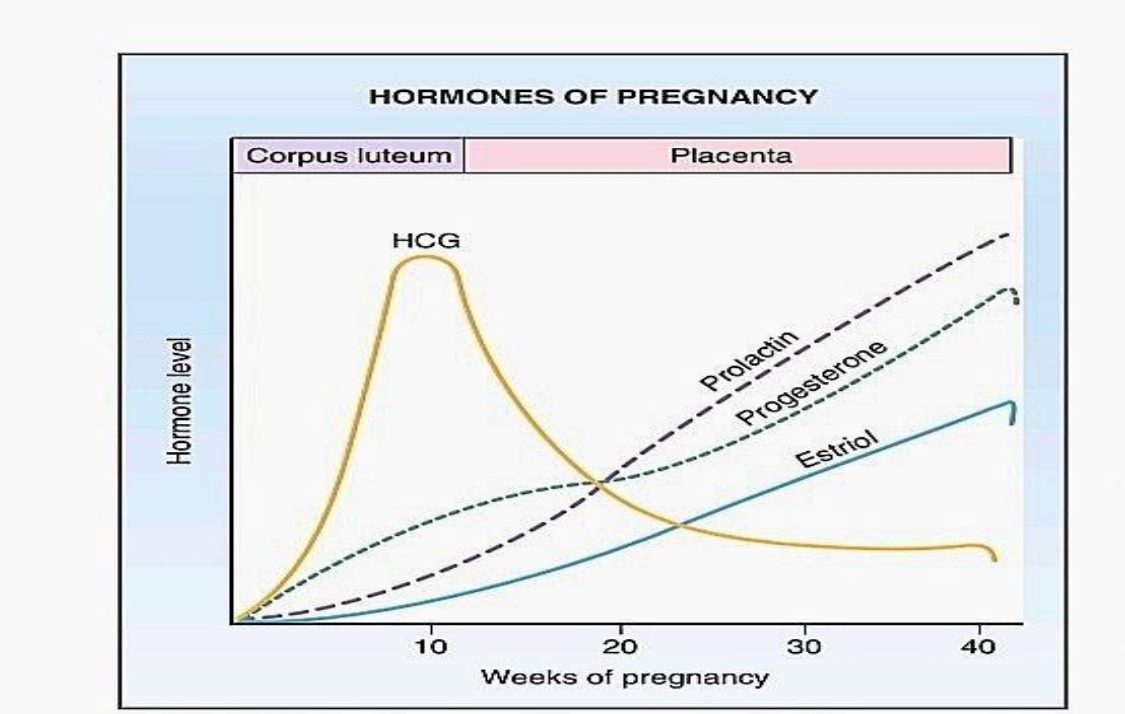


Fig 7 : Hormones of pregnancy. Number of weeks of pregnancy are counted from the onset of the last menses *HCG* Human chronic gonadotropin (Physiology sixth edition By Linda S. Costanzo, 2018).

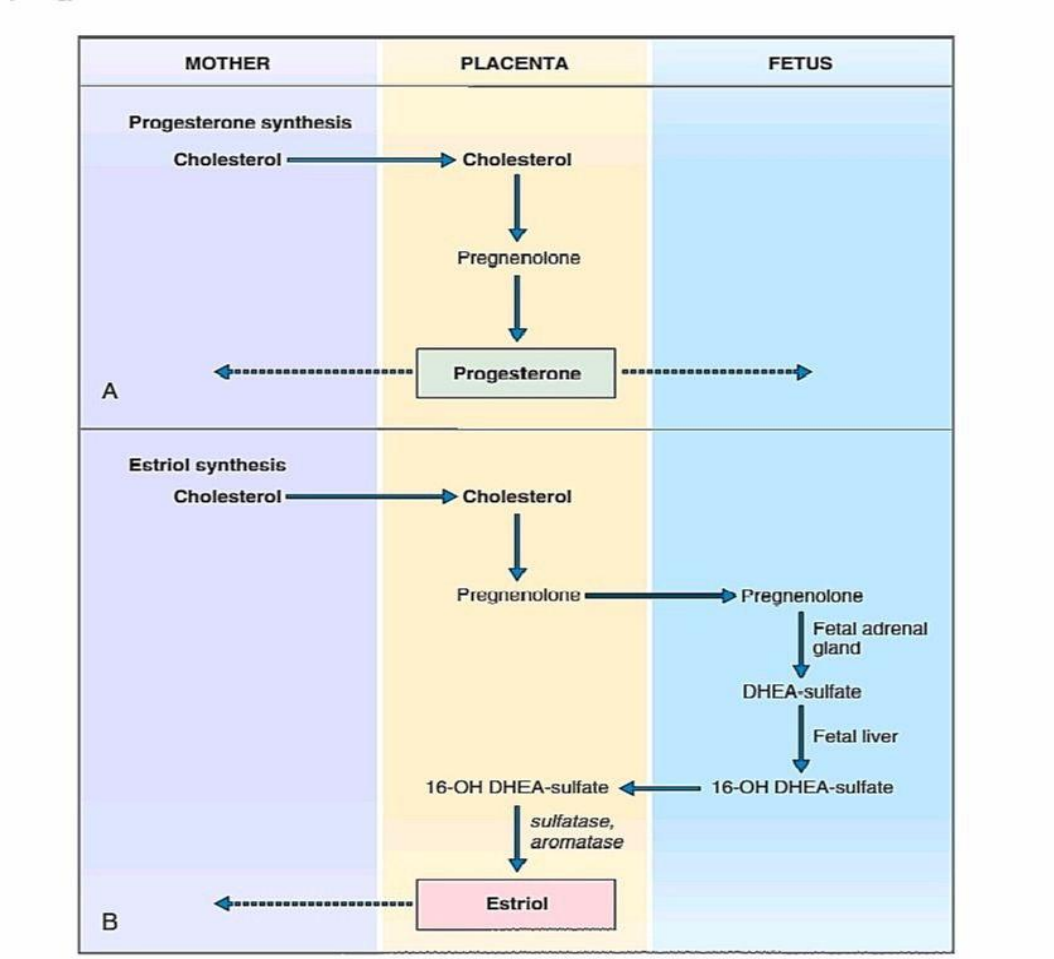


Fig 8 : Synthesis of progesetrone (A) and estriol (B) during pregnancy . pregsterone is synthesized entirely by the placenta . Estriol synthesis requires the placenta . the fetal adrenal gland ,and the fetal liver .*DHEA* ,Dehydroepiandrosterone (Physiology sixth edition By Linda S. Costanzo, 2018).

3.5 Other hormones

3.5.1 Gonadotropin-releasing hormone (GnRH), FSH, and LH, primary mediators of sex hormones releasing

The GnRH is a hormone synthesized by the hypothalamic neurons. It travels through the portal-pituitary-system to bind to its receptors (GnRHR-I) in pituitary cells (gonadotrophs), activating the synthesis of FSH (Follicle-stimulating hormone) and LH (Luteinizing hormone). These hormones are released into the systemic circulation to act on sex organs regulating both

oogenesis and spermatogenesis. Interestingly, GnRH isoforms (GnRH-I and GnRH-II) have also been identified in other tissues, including the testicles, prostate, mammary gland, endometrium, and placenta. In these organs, it has been shown that GnRH-II acts by binding to GnRHR-II receptors(Sasaki K, Norwitz ER,2011) . The functions associated with these isoforms are the production of the β-human chorionic gonadotropin (β-hCG) by the syncytiotrophoblast in the early stages of pregnancy. Here, β-hCG intervenes in at least two vital functions, avoiding luteolysis and ensuring Progesterone's production (P4) until the placenta is implanted. Thus, specific conditions that interfere with this endocrine axis before weeks seven to nine of gestation would culminate in pregnancy loss(Sasaki K, Norwitz ER 2011). Moreover, recent evidence indicates that GnRH is involved in the maternal-fetal environment's remodeling (milieu) that allows the fetus's correct implantation. Preclinical studies have shown that both isoforms (GnRH-I and GnRH-II) modify cellular matrix metalloproteinases' expression. Two of them, MMP-2 and MMP-9, are the most directly involved in the migration and invasion of trophoblasts(Sasaki K, Norwitz ER ,2011). GnRH's direct participation is vital for all physiological, hormonal, and structural changes that will culminate in the fetus's correct implantation. On the other hand, GnRH causes the stimulation of the pituitary hormone's LH and FSH to regulate the sexual function. However, preclinical studies showed that both hormones are inhibited because of Progesterone and Estrogen increased production during pregnancy. Moreover, FSH and LH level rises on day ten after birth, (Hirano M, Igarashi A, Suzuki M. ,1976) .

3.5.2 The modulatory hormones in pregnancy; testosterone (T), androstenedione (A4), and dehydroepiandrosterone (DHEA)

The androgenic hormones T, A4, and DHEA, plays a central role in regulating reproductive processes in many mammalian species. Besides, the presence of androgen receptors has also been demonstrated in different tissues such as the ovary, the myometrium, and placenta, where they are known to participate in implanting the fetus and placentation. In this sense, it has been shown that, once pregnancy occurs, androgen synthesis takes place in the small luteal cells (SLC) of the corpus luteum by stimulation of the human chorionic gonadotrophin (hCG) (Costa MA,2015 and Makieva S, Saunders PT, Norman JE.,2014) . In addition to the above, once the placenta has been established, it becomes an independent androgen production source

(Makieva S, Saunders PT, Norman JE.,2014) In this aspect, placental syncytiotrophoblast uses the circulating DHEA, provided by the maternal and fetal adrenal glands, turning it into A4 and T. Which, in turn, can be converted to estrogens by different routes to regulate embryonic development (Costa MA,2015 and Satué K, Marcilla M, Medica P, Ferlazzo A, Fazio E.,2018) . Interestingly, it has been suggested that myometrium could be another important source of androgens during pregnancy; a recent in vitro study showed that this tissue could also produce T and A4 (Satué K, Marcilla M, Medica P, Ferlazzo A, Fazio E.,2018) . Suppressively, these hormones are coordinated synthesized during pregnancy. Specifically, it has been shown that T levels increase in the first trimester of pregnancy, reaching a plateau in the second trimester, to later decrease slightly, rising considerably in the last month of pregnancy . Concerning A4, the study carried out by Satué et al. (2018) in mares shows that this hormone rises during gestation, from the second month of pregnancy, reaching a peak maximum in the first stage of pregnancy, and, in the second state, it reduces significantly, reaching its lowest levels in the last month of gestation. However, a clinical study conducted by Makieva et al. (2014) showed that A4 remains stable throughout pregnancy without significant fluctuations. About DHEA, it increases progressively from the first to the fifth month of pregnancy, reaches its highest levels, then begins to decrease between months 6 and 7, reaching its lowest levels in the last month of pregnancy in mares, which is agree with the observed in pregnant women, with levels up to 50% lower than those observed in non-pregnant women, (Makieva S,et al.2014 Satue et al. 2018).

3.5.3 Cortisol and glucocorticoids

The secretion of cortisol levels during pregnancy is regulated by the placenta, which, by secreting the corticotropin-releasing hormone (CRH), produces an exponential increase in cortisol from the eighth week of gestation up to three times above systemic values (Sasaki K, Norwitz ER,2011 and Field T, Diego M.,2008) It is present in both the maternal and fetal phases but at different levels; under normal conditions, cortisol levels reach 200 ng/ml at the end of pregnancy, while fetal levels range from around 20 ng/ml(Shams M,et al.1998). These differences are due to the presence of a natural barrier that prevents maternal cortisol, whose molecular composition can cross the placenta, quickly reaches fetal space(Diego MA ,et.al 2006,Chan J, 2007). However, because of its role in organ maturation and labor, fetal cortisol increases towards the end of pregnancy by several mechanisms: a) decrease of 11-β-HSD type 2

in fetal tissues, b) increased synthesis of cortisol by the fetal adrenal gland, and c) increased 11-β-HSD type 1 in fetal tissues, which converts cortisone, into active cortisol (Myatt L, Sun K, 2010). As for the functions of cortisol during pregnancy, glucocorticoids (GC) have been described as participating in the processes of implantation and formation of decidua, as well as in fetal development and maturation, and initiation of childbirth (Chang K, Lubo Zhang, 2008, Field T, Diego M,2008, Rosen T, et.al. 1998) Elevated levels of GC present during pregnancy are involved in the suppression of inflammation of the uterus, placenta, and fetal membranes, which contributes to maintaining the homeostasis necessary for the maintenance of pregnancy (Rosen T, et.al. 1998). Moreover, recent evidence suggests that significant increases in cortisol levels play a critical role in the baby's growth in the postnatal stage (Street ME, et.al., 2012). In this sense, studies have shown that high concentrations of cortisol during the fetal phase positively correlated with weight gain within the first five years of postnatal growth, indicating that the higher increase in placental cortisol levels, the more significant weight gain can be observed in children during this stage (Street ME, et.al., 2012). Conversely, cortisol is also involved in developing pregnancy complications, being responsible for the so-called "Hypothalamic Stress Amenorrhea," whose consequence is the generation of miscarriages (Arck P, Hansen PJ, Mulac Jericevic B, Piccinni MP, Szekeres-Bartho J. 2007, Tian CF, Kang MH.2014). On the one hand, it has been shown that low maternal cortisol levels compromise the placenta's structure. In contrast, elevated levels can lead to miscarriages, uterine contractions from placental CRH deregulation, the elevation of fetal cortisol levels, and obstetric alterations by activation of the HPA gland axis (Makieva S, Saunders PT, Norman JE ,2014, Field T, Diego M.,2008, Diego MA, 2006, Marsman R, Rosmalen JG, Oldehinkel AJ, Ormel J, Buitelaar JK, 2009) .

Chapter Four

Chapter four: The Impact Of Hormonal Change On Periodontium

4.1 Periodontal Changes during Pregnancy

Recent cross-sectional and longitudinal studies have further confirmed and extended the association between pregnancy and gingival condition in many cultural and ethnic groups. In 2000, a group of researchers reported the findings of the study including 47 pregnant women and 47 nonpregnant women who served as matched controls in a rural population of Sri Lankans [a tilakaratne and et al 2000]. The periodontal status of the pregnant women was evaluated in the first, second, and third trimester of pregnancy and the final examination was at three months postpartum. The authors found that although the plaque levels remained unchanged, the gingival index (GI) of pregnant women was significantly increased and peaked in the third trimester but dropped at 3 months postpartum [atilakaratne and et al 2000].The results were consistent with the findings of another cohort study in 2003 consisting of 200 pregnant women and 200 nonpregnant controls in Jordan [d.q taani and et al 2003]. In this study, it was reported that pregnant women had significantly higher GI and periodontal pocket depth (PPD) with similar plaque index (PI) compared with nonpregnant women. The clinical parameters (PPD and GI) increased in parallel with the increase in the stage of pregnancy, which reached the maximum at the eighth month [d.qtaani and et al 2003]. In another companion study with a smaller sample size of 19 pregnant women, bleeding on probing (BOP) decreased from 41.2% at the twelfth week of pregnancy to 26.6% postpartum without any active periodontal therapy [Bieri and et al 2013]. From these studies, the increased inflammation was detected in the gingival region rather than in other periodontal sites, indicating that pregnancy only has reversible effect on the gingiva without inducing periodontal attachment loss. It could be speculated that periodontal attachment loss requires a chronic inflammatory state of the gingiva lasting longer than pregnancy when the gingival changes occur [M.Alian and et al 2002]. However, this speculation remains to be proved. Some results showed that attachment loss was significantly greater in the users of .combined oral contraceptives (COC) compared to the nonusers [B.H mullay and et al 2007]

Recent studies further confirmed that gingivitis associated with pregnancy seemed to be dependent on, but unrelated to, the amount of dental plaque accumulation [G.c armitage and et al 1999]. It seemed that good oral hygiene in pregnancy was able to partially neutralize hormonal

effect [G klinger and et al 1998]. Although, as it is well known, periodontal diseases have been considered to be microorganisms initiated, whether pregnancy's influence on gingival tissue might be independent or pregnancy by itself would cause new gingivitis has been proposed. Two most recent cohort studies were performed according to this proposal. Differed from those studies described above, these studies included the healthy periodontium without any gingival inflammation and excellent oral hygiene marked with fairly low plaque index in the subject criteria. One of these studies followed 48 pregnant Spanish women with healthy periodontium and examined their periodontal index in the first, second, and third trimesters and at 3 months postpartum. Despite maintaining fairly low Pl values, the pregnant women showed an increase in GI which maintained high levels in the third trimester and then decreased at 3 months postpartum [E.figuero and et al 2010]. In the other longitudinal study, the authors described the development of gingival inflammation in 30 periodontally healthy pregnant women with good oral hygiene in Finland. They found that the increase in gingival inflammation evaluated by BOP and the number of deep periodontal pockets (PPD $\geqslant$ 4 mm) in pregnant women was not related to dental plaque simultaneously between the first and second trimesters, followed by a decrease afterwards [M gursoy and et al 2008] Periodontium is a unique structure composed of two fibrous (gingival and periodontal ligament) and two mineralized (cementum and alveolar bone) tissues [B.L mealey and et al 2003]. For the reason that pregnancy probably has an effect only on the gingiva and has no permanent effects on periodontal attachment, meantime, the effect of female sex hormones on periodontal ligament and tooth supporting alveolar bone has rarely been investigated [P.mishra and et al 2013]

4.2 Pyogenic granuloma (PG)

Is a benign connective tissue proliferation that is predominantly characterized by granulation tissue hyperplasia, and it occurs frequently in the skin or mucous membranes [gomes,Shakir et. al 2013]. It is considered one of the most common lesions responsible for soft tissue enlargements, due to its rapid and alarming growth rate [ghalayani ,hajisadegi et al 2014] Pyogenic granuloma (PG) was first described in 1897 by Poncet and Dor, who reported -four patients with “vascular tumors” on the fingers which they named “Botrichomycosis ho minis” [poncet. et al 1897]. The term “pyogenic granuloma” was introduced in 1904 by Hartzell. However, the name is considered inappropriate as it is neither related to pus formation, nor is it

histologically a true granuloma [gomes,shakir et .al 2013]. Due to the controversy regarding its true pathological nature, this lesion has been given several names such as granuloma pediculatum benignum, benign vascular tumor, septic granuloma, hemangiomatous granuloma, vascular epulis, fibroangioma, polypoid capillary hemangioma, eruption capillary hemangioma non-lobular capillary hemangioma, and Crocker and Hartzell's disease [kamal,dahiya and et.al 2012]. In pregnant women, GP is identified as pregnancy granuloma, pyogenic granuloma of pregnancy, or granuloma gravidarum [winer, winer pla and et.al 2014].

4.2.1 Etiopathogenesis

Some factors are implicated in the etiopathogenesis of PG. However, the exact cause is unknown. Historically, some researchers consider it to be a pathology attributable to an infectious agent, hence the term "pyogenic" [kamal and et. al 2012]. Kerr in 1951 was of the view that the factors that influence the progression of PG were bebotryomycosis, staphylococci, foreign particles, and the accumulation of infection in the endothelium of blood vessels [kerr and et.al 1951]. In a study by Bhaskar and Jacoway, Gram-positive and Gram-negative bacilli were identified in GP. However, these microorganisms could be members of the oral microbiota, since they were more frequent in ulcerated lesions than in non-ulcerated lesions [Bhaskar and et.al 1966]

Several researchers define the PG as a "reactive" or "reparative" process. Regezi et al. consider PG a reactive or repairing process in which a certain stimulus generates an exuberant proliferation of connective tissue [gomes and et.al 2013]. The etiological factors considered as stimuli that trigger this reactive process are trauma, dental calculus, dental biofilm, chronic irritation, pre-existing vascular lesions, chronic irritation due to exfoliation of primary teeth, injury of a primary tooth, eruption of permanent teeth, defective restorations in the area of the lesion, occlusal interference, food impaction, periodontitis, and trauma from toothbrushing [al-noman and et al 2020].

Pyogenic granuloma (PG) may manifest after a hypersensitivity reaction associated with the use of drugs such as calcineurin inhibitors (cyclosporine and tacrolimus), carbamazepine, phenytoin, nifedipine, levothyroxine and ramucirumab [piraccini and et.al 2010 and aragaki and et.al 2021].

Additionally PG is associated with retinoid, antineoplastic and antiretroviral agents [piraccini and et.al 2010] In pregnancy in particular, these hormonal changes have been associated with vascular, microbiological, cellular and immunological modifications which generate a favorable environment for the initiation and development of PG [silva de araujo and et. al 2017].

The hormones estrogen, progesterone and chorionic gonadotropin induce certain alterations in the microcirculatory system, including swelling of endothelial cells, increased adhesion of platelets and leukocytes to vessel walls, formation of microthrombi, disruption of perivascular mast cells, increased vascular permeability, and vascular proliferation [Figuero-ruiz and et. al 2006] The imbalance between angiogenesis enhancers and inhibitors is one of the hypotheses for the etiopathogenesis of PG. It highlights the important role of certain factors such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), tyrosine kinase with immunoglobulin-like, EGF-like domains-2 (Tie-2), angiopoietin-1 (Ang-1),angiopoietin-2 (Ang-2), ephrin-B2 and Eph-B4 in the processes involved in adult inflammatory neovascularization [yuan and et al 2000]. On the other hand, Shetty et al. reported that PG is triggered by the presence of local and/or systemic factors that generate the release of various endogenous substances (tumor cell angiogenic factors and vascular morphogenic factors), leading to alterations in the vascular system of the affected area [shetty and et al 2020]

-Mast cells release mediators that increase vascular permeability and vasodilation, facilitating the migration of inflammatory cells . The outcome of mutual mast cell–fibroblast interactions promotes granulation tissue formation, a hallmark of PG [komi and et.al 2020].

4.2.2 Clinical Features

Pyogenic granuloma (PG) occurs most often in the skin or in the oral cavity, but rarely in the gastrointestinal tract, trachea, urinary bladder, and central nervous system [Yao and et al .1995]

In the oral cavity, the gingiva accounts for 75% of the sites of predilection of this pathology However, PG may occur in other areas such as the lips, tongue, buccal mucosa, hard plate and peri-implant mucosa, and it affects the maxilla more than the mandible, the anterior region more than the posterior region as shown in (figure 9), with the buccal surfaces more affected than the lingual surfaces [sharma and et al 2019].

In the literature, the floor of the mouth is not considered as a site of occurrence of PG. This is perhaps due to the fact that in addition to the absence of sufficient amounts of connective tissue in the mucosa of the floor of the mouth, the tongue protects this region from traumatic injury [akyol and et al 2016].

Oral PG is a pathology that manifests as a raised, smooth or exophytic growth on a sessile or pedunculated broad base with a smooth and lobulated surface covered with red ,hemorrhagic and erythematous compressible papules which appear lobulated and warty complete with ulcerations and covered by a yellow brackish membrane . The surface of the pathology is frequently ulcerated in areas subjected to trauma, and due to its pronounced vascularity, occasional bleeding may occur, especially during mastication. The clinical course of PG is generally slow, asymptomatic and painless [leung and et al 2014]. The growth of PG is slow, and it takes from weeks to months to reach optimal size . The size of PG may vary in diameter from a few millimeters to several centimeters [jafarzadeh and et al 2006]. The color of this pathology depends on its age: younger PGs tend to be reddish due to the large number of blood vessels, while older ones appear pink in color. The consistency of the oral PG depends on the age of the lesion: as the lesion matures, collagen fibers increase in number, and the lesion becomes firm [Nejad and et.al 2014].

The signs and/or symptoms referred to by the PG patients in anamnesis are bleeding. [aguilo and et.al 2002], difficulty in chewing [ganesan and et.al 2015], and pain and tenderness [Behl ,bali and et. al 2011].

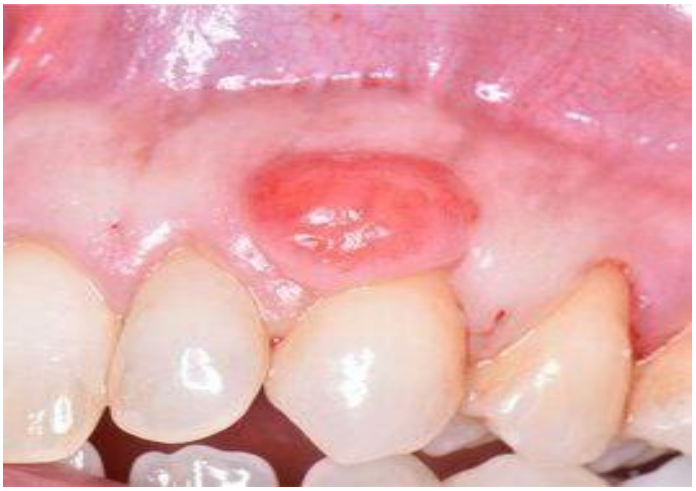


Fig 9: pyogenic gralnuloma (Bhashkar SN, Jacoway JR. Pyogenic granuloma: clinical features, incidence, histology, and results of treatment report of 242 cases. J Oral Surg. 1966;24:391).

4.2.3 Treatment of oral PG

The treatment or the management of oral PG depends on the particular characteristics presented by each patient. However, the treatment of choice is conventional surgical excision. Other minimally invasive treatment modalities have been suggested, including laser, corticosteroid injections, cryosurgery and sclerotherapy [leung and et al 2014] Surgical excision consists of the complete removal of the lesion and the extension of the cut to the periosteum, including a 2 mm margin to the adjacent soft tissues. If the -PG is located near adjacent teeth, it is important that after removal of the lesion, debridement is performed both supra- and sub-gingivally to the biofilm and/or dental calculus Additionally, it is important to remove all irritating agents (foreign materials, sources of trauma, overhang crowns, etc.) that are present in the area of the lesion. These suggested measures, both in the surgical technique and in the removal of irritants, are aimed at avoiding recurrence of PG [Rosa and et al 2017].

Chandrashekar implemented a minimally invasive approach as a treatment strategy for oral PG. This protocol consists of performing scaling and root planning in the area where the lesion is located. In addition, it is crucial to maintain complete oral hygiene by brushing twice a day and using a 0.12% chlorhexidine rinse twice a day. It is necessary to monitor the evolution of the lesion every week. If the lesion persists, scaling and root planning should be implemented every week for four consecutive weeks in order to continue with the non-invasive approach. At the same time, it is recommended that patients should maintain adequate brushing and flossing twice a day. This minimally invasive treatment may be considered when the PG is small in size, painless, and without bleeding [chandrashekar and et al 2012].

4.2.4 Alterations in Subgingival Microbiota

It is widely agreed that the majority of tissue damage in gingivitis and initial periodontal lesions occurs via an inflammatory response of the host to the presence of microbes, their structural and metabolic products, and the products of affected tissues themselves [J.W .smally and et al 1994].Periodontium acts as a reservoir of subgingival bacteria Changes in the subgingival microbiota have been proposed as a potential mechanism for exacerbated gingival inflammation

during pregnancy. In this regard, it should be kept in mind that there are three classic works of research in the early eighties of the last century. In one longitudinal study of 20 pregnant women, Kornman and Loesche were the first to report statistically significant increases in the levels of Bacteroides intermedius during the second trimester, with a reduction during the third trimester and after delivery The marked increase in the proportion of the bacteria seemed to be associated with increased serum levels of progesterone or estrogens which substituted for the naphthaquinone requirement of the pathogens and thus acted as a growth factor for the bacteria [A.Mariotti anzd et al 1994]. The authors explained the reason of the growth of Campylobacter rectus as formate enhancement from the growth of Prevotella intermedia that was stimulated by direct interaction of female sex hormones on the fumarate reductase system. Also, another study showed that the growth of Campylobacter rectus was significantly enhanced gingival fibroblasts (HGF) [M.Yokoyama and et al 2005]

It should be noted that the bacteria known as Fusobacterium nucleatum were referred to in some aforementione studies. As an opportunistic oral bacterium, it is associated with various forms of periodontal diseases, including gingivitis. Recently, Fusobacterium nucleatum has been gaining increasing attention because of its association with adverse pregnancy outcomes. It is capable of invading not only gingival epithelial cells, gingival fibroblasts, and periodontal ligament fibroblasts, but also other different types of human cells [Y.W .Han and et al 2000].

4.3.4 Alveolar bone health

Pregnancy hormones may influence bone metabolism and decrease the body's ability to regenerate alveolar bone. Increased bone resorption and a reduction in bone density can make the alveolar bone more susceptible to destruction from periodontal disease. The combination of hormonal effects and periodontal disease progression can thus increase the risk of tooth mobility and eventual tooth loss, (figure 11)shows vertical angular bone defect [shoji k and et al 2002].

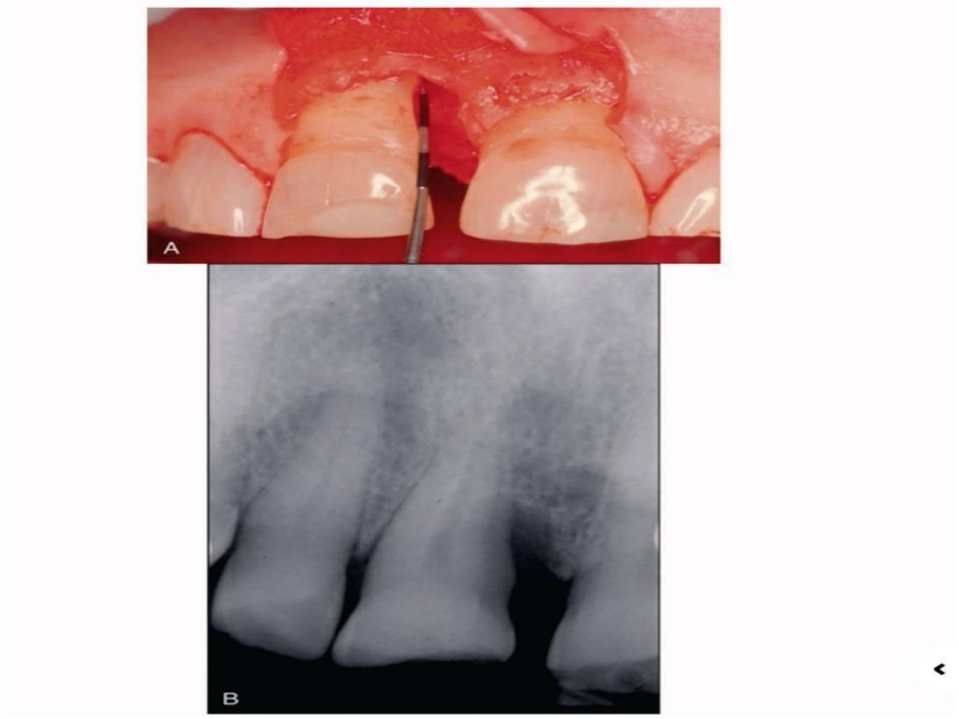


Fig 11 :(A) clinical photo , (B) radiographic photo for vertical angular bone defect (Favero V, Bacci C, Volpato A, Bandiera M, Favero L, Zanette G. Pregnancy and dentistry: a literature review on risk management during dental surgical procedures. Dent J. (2021)

4.4 Best timing for dental treatment during pregnancy

The second trimester (weeks 13–27) is considered the safest time for most dental treatments during pregnancy. At this stage, the risk of miscarriage is lower, and the baby's organs have already formed. Dental treatments such as fillings, crowns, and even certain extractions are generally considered safe, but non-essential treatments such as ,cosmetic procedures, should be avoided.

First trimester: During the first trimester, dental treatments that are not urgent should be postponed to avoid any potential risks to fetal development. The first weeks are critical for the development of the baby's organs and tissues, and the risk 12 of teratogenic effects from medications, anesthetics, or radiation is higher [shoji k and et al 2002]

Third trimester: The third trimester is a less ideal time for dental procedures due to the physical discomfort that may accompany lying back in the dentist's chair and the potential for higher blood pressure or gestational hypertension. However, necessary treatments such as tooth extractions or infection control may still be performed if urgent [hemalatha and et al 2013].

Appropriate supplementation of a variety of nutrition during pregnancy has become an effective way to prevent periodontal disease and adverse pregnancy outcomes the management of periodontal infection during pregnancy should follow relevant treatment principles, and the ideal time for periodontal treatment is the ,second trimester (14–27 weeks). If intervention for infection is absolutely necessary emergency treatment can be performed throughout pregnancy [Nannan and et al 2022].

4.5 Considerations during pregnancy

Dental X-rays should be avoided unless absolutely necessary. If an X-ray is required, a lead apron should be used to shield the abdomen. Modern digital X-rays expose the body to much lower levels of radiation than traditional methods, which reduces risks, but it is still advisable to postpone elective X-rays during pregnancy Local anesthetics such as lidocaine with epinephrine are commonly used during dental procedures and are generally considered safe during pregnancy. However, care should be taken to avoid excessive amounts of epinephrine, as it may cause vasoconstriction, affecting blood flow to the fetus, Penicillin and its derivatives (such as amoxicillin) are considered safe during pregnancy and are commonly prescribed for oral infections; also, the metronidazole has similar condition. Clindamycin is another safe alternative for treating infections Tetracyclines should be avoided during pregnancy as they can affect fetal bone development and teeth discoloration. As an analgesics, the acetaminophen is the safest pain killer during pregnancy, and the ibuprofen is safe also except in the 3th trimester [Hemalatha and et al 2013]

4.6 Effects of Estrogen on the Periodontal Tissues

-Decreases keratinization while increasing epithelial glycogen that results in the diminution in the effectiveness of the epithelial barrier[MANSON JD and et al 2004]
-Increases cellular proliferation in blood vessels[lindhe j and et al 1967]
-Stimulates PMNL phagocytosis[Hofman R and et al 1986]
-Inhibits PMNL chemotaxis[Ito and et al 1995]
-Suppress leukocyte production from the bone marrow [josesson and et al 1992]
-Inhibits proinflammatory cytokins released by human marrow cells[gordon and et al 2001]

-Reduces T-cell mediated inflammation

-Stimulates the proliferation of the gingival fibroblasts[jossefsson and et al 1992]

-Stimulates the synthesis and maturation of gingival connective tissues[Beagrie gs and et al 1966]

-Increases the amount of gingival inflammation with no increase of plaque.[Reinhardt and et al 1999].

4.7 Effects of Progesterone on the Periodontal Tissues

-Increases vascular dilatation, thus increases permeability [Mascarenhas and et al 2003]

-Increases the production of prostaglandins [Elattar Tm and et al 1976]

-Reduces glucocorticoid anti-inflammatory effect [chen Tl and et al 1977]

-Inhibits collagen and noncollagen synthesis in PDL fibroblast [telakaratani and et al 1999]

- Inhibits proliferation of human gingival fibroblast proliferation

-Alters rate and pattern of collagen production in gingiva resulting in reduced repair and maintenance potential [Mealey and et al 1982]

-Increases the metabolic breakdown of folate which is necessary for tissue maintenance and repair. [thomson and et al 1982].

Conclusion

Hormonal changes during pregnancy have a profound impact on the periodontium, which encompasses the structures that support teeth, These effects are through either reducing protection factors, for example decreases keratinization while increasing epithelial glycogen that results in the diminutionin the effectiveness of the epithelial barrier, Increases the metabolic breakdown of folate which is necessary for tissue maintenance and repair, inhibtion of (chemotaxis, pro inflammtory cytokines and proliferation of fibroblasts) OR by increasing inflammatory factors like Increases vascular dilatation, thus increases permeability, Increases the Production of prostaglandins, Increases the amount of gingival inflammation with minimal plaque This thus leads to development conditions like pyogenic granuloma, increased bone resorption, tooth mobility etc .

So Pregnant women require comprehensive dental care and education to mitigate the adverse effects while supporting their oral health needs. Enhanced awareness among healthcare providers about the specific risks associated with pregnancy-related hormonal changes is essential for promoting both maternal and fetal health, and future research should focus on developing effective preventive measures and treatment protocols for maintaining periodontal health during this critical period..

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