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In the

Salivary cortisol change in women patient with threatening abortion

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((وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ))

SUPERVISOR CERTIFICATION:

I certify that the preparation of this project entitled "Salivary cortisol changes in women patient threatening abortion". Prepared by:

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Was made under my supervision at Department of Oral Diagnosis in partial fulfillment of the Requirements for the Degree of Bachelor of Science in Dentistry.

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Dedication:

To my parents that support and help me in every step of my life and give me the greatest love...

To all my previous teachers and any one that give me any information to reach for this level...

To my supervisor for his guidance helpness and endless support throughout this project.

Introduction

Abortion:

Is defined as the loss of pregnancy before foetal viability i.e. before a foetus becomes capable of independent extra-uterine life .An induced abortion, also known as a termination of pregnancy, is an abortion initiated by deliberate action undertaken with the intent of terminating pregnancy .A spontaneous abortion is one which is not induced, even if an external cause is involved such as trauma or communicable disease .An unsafe abortion is defined by the WHO as "the termination of an unintended pregnancy either by persons lacking the necessary skills or in an environment lacking the minimum medical standards or both."

(Ganarata et al., 2010)

"The persons, skills and medical standards considered safe in the provision of abortion are different for medical and surgical abortion and also depend on the duration of the pregnancy. What is considered 'safe' should be interpreted in line with current WHO technical and policy guidance."

The abortion is "expulsion of the fetus before it is viable." This could include spontaneous abortion (miscarriage) or induced abortion, in which someone (a doctor, the woman herself, or a layperson) causes the abortion. **(say et al.2014)**

Before modern methods of abortion, this sometimes meant the introduction of foreign objects such as catheters into the uterus to disrupt the placenta and embryo (or fetus) so that a miscarriage would result. In preindustrial societies, hitting

The pregnant woman in the abdomen over the uterus and jumping on her abdomen while she lies on the ground are common techniques used to induce an abortion **(Early & Peters 1990)**. Although these methods can be effective, they may also result in death of the woman if her uterus is ruptured or if some of the amniotic fluid surrounding the fetus enters her blood stream

(Bearak et al., 1990)

From the Colonial period to the early twentieth century in America, primitive methods such as these were used along with the introduction of foreign objects into the uterus (wooden sticks, knitting needles, catheters, etc.) to cause abortion, frequently with tragic results **(Lee 1969)**.

In modern American society, abortions are performed surgically by physicians or other trained personnel experienced in this technique, making the procedure much safer than when primitive methods were used. The goal of induced abortion still remains the same: Interrupt the pregnancy so that the woman will not continue to term and deliver a babe. One problem with the classical definition of abortion is the changing definition of viability (the ability to live outside the womb). Premature birth is historically associated with high death and disability rates for babies born alive, but medical advances of the twentieth century have made it possible to save the lives of babies born after only thirty weeks of pregnancy when the usual pregnancy lasts forty weeks. Some infants born at twenty-six to twenty-seven weeks or even younger have survived through massive intervention and support. At the same time, abortions are now sometimes performed at up to twenty-five to twenty-six weeks of pregnancy. Therefore, the old definition of viability is not helpful in determining whether an abortion has been or should be performed

(Main et al., 1985).

Cortisol:

Though widely known as the body's stress hormone, Cortisol has a variety of effects on different functions throughout the body. It is the main glucocorticoid released from the zona fasciculata layer of the adrenal cortex. The hypothalamus-pituitary-adrenal axis regulates both production and secretion of cortisol. Loss of regulation can lead to cortisol excess disorders, such as Cushing syndrome, or cortical insufficiency, such as Addison disease.

Cortisol, a steroid hormone, is synthesized from cholesterol. It is synthesized in the zona fasciculata layer of the adrenal cortex. Adrenocorticotropic hormone (ACTH), released from the anterior pituitary, functions to increase LDL receptors and increase the activity of cholesterol desmolase, which converts cholesterol to pregnenolone and is the rate-limiting step of cortisol synthesis. The majority of glucocorticoids circulate in an inactive form, bound to either corticosteroid-binding globulin (CBG) or albumin.The inactive form is converted to its active form by 11-beta-hydroxysteroid dehydrogenase 1 (11-beta-HSD1) in most tissues, while 11-beta-HSD2 inactivates cortisol back to cortisone in the kidney and pancreas.

Glucocorticoid receptors are present in almost all tissues in the body. Therefore, cortisol is able to affect nearly every organ system:

- Nervous

- Immune
- Cardiovascular
- Respiratory
- Reproductive
- Musculoskeletal
- Integumentary

Cortisol has many functions in the human body, such as mediating the stress response, regulating metabolism, the inflammatory response, and immune function.

Glucocorticoids have a number of actions in the immune system. For example, they induce apoptosis of proinflammatory T cells, suppress B cell antibody production, and reduce neutrophil migration during Inflammation. **(Angelousi et al., 2020)**

The human body is continually responding to internal and external stressors. The body processes the stressful information and elicits a response depending on the degree of threat. The body's autonomic nervous system is broken down into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS).

In times of stress, the SNS gets activated. The SNS is responsible for the fight or flight response, which causes a cascade of hormonal and physiological responses. The amygdala is responsible for processing fear, arousal, and emotional stimuli to determine the appropriate response. If necessary, the amygdala sends a stress signal to the hypothalamus. The hypothalamus subsequently activates the SNS, and the adrenal glands release a surge of catecholamines, such as epinephrine. This results in effects such as increased heart rate and respiratory rate. As the body continues to perceive the stimuli as a threat, the hypothalamus activates the HPA axis. Cortisol is released from the adrenal cortex and allows the body to continue to stay on high alert. Acutely, cortisol's catabolic mechanisms provide energy to the body.

Blood glucose levels drive key systemic and intracellular pathways. The presence of glucocorticoids, such as cortisol, increase the availability of blood glucose to the brain. Cortisol acts on the liver, muscle, adipose tissue, and pancreas. In the liver, high cortisol levels increase gluconeogenesis and decrease glycogen synthesis. Gluconeogenesis is a metabolic pathway that results in the production of glucose from glucogenic amino acids, lactate, or glycerol 3- phosphate found in triglycerides. Gluconeogenesis reverses glycolysis, a cytoplasmic pathway used to convert glucose into pyruvate molecules. This pathway is used to release energy through substrate-level phosphorylation and oxidation reactions. Unlike glycolysis, gluconeogenesis

becomes active when the body needs energy. Muscles have their own internal glycogen supply that allows them to respond to changes in ATP requirements rapidly. In the presence of cortisol, muscle cells decrease glucose uptake and consumption and increase protein degradation; this supplies gluconeogenesis with glucogenic amino acids. In adipose tissues, cortisol increases lipolysis. Lipolysis is a catabolic process that results in the release of glycerol and free fatty acids. These free fatty acids can be used in B oxidation and as an energy source for other cells as they continue to produce glucose. Lastly, cortisol acts on the pancreas to decrease insulin and increase glucagon. Glucagon is a peptide hormone secreted by the pancreatic alpha cells to increase liver glycogenolysis, liver gluconeogenesis, liver ketogenesis, lipolysis, as well as decreases lipogenesis. Cortisol enhances the activity of glucagon, epinephrine, and other catecholamines.

(Kuo and McQueen, 2015)

Threating abortion

Abortion is the medical term for a pregnancy loss before 20 weeks of gestational age. The types of spontaneous abortion include threatened, inevitable, incomplete, complete, septic, and missed abortion **(Alves, and Rapp, 2022)**

A threatened abortion is defined as vaginal bleeding before 20 weeks gestational age in the setting of a positive urine and/or blood pregnancy test with a closed cervical os, without passage of products of conception and without evidence of a fetal or embryonic demise. The definition of a threatened abortion by the World Health Organization (WHO) is pregnancy-related bloody vaginal discharge or frank bleeding during the first half of pregnancy without cervical dilatation.

Other types of abortion should be considered if the cervical os is open, if there is determined to be an extrauterine pregnancy, if there is determined to be an intrauterine pregnancy without a fetal heartbeat, or if there is evidence of the passage of products of conception.

Nearly 25% of pregnant women have some degree of vaginal bleeding during the first two trimesters and about 50% of these progress to loss of the pregnancy. The bleeding during a threatened abortion is typically mild to moderate. The abdominal pain may present as intermittent cramps, suprapubic pain, pelvic pressure, or lower back pain. **(Karataşl et al., 2019)**

Epidemiology

Threatened abortion can occur in any pregnancy regardless of maternal age, race, comorbidities, lifestyle, or socioeconomic status. If a woman has previously had bleeding in the first trimester of pregnancy, her risk of bleeding in the first trimester of subsequent pregnancies does appear to be increased. Risk factors for any type of miscarriage include advanced maternal age, advanced paternal age, prior history of pregnancy loss, TORCH infections, uncontrolled hyperglycemia, obesity, uncontrolled thyroid disease, significant stressors, use of teratogenic medications, and presence of a subchorionic hemorrhage **(du Fossé et al., 2020)**.

Causes

- Embryo is implanting.
- Infection.
- Irritation that may occur after sex.
- Miscarriage.
- The baby grows outside the uterus ectopic pregnancy.
- Molar pregnancy—a rare growth in the uterus

The exact etiology of a threatened or spontaneous abortion is not always known. It is widely accepted that the vast majority of spontaneous abortions cannot be prevented or modified likely because they are due to chromosomal abnormalities in at least half of all cases. For pregnancy losses that are determined to have a normal chromosomal makeup, termed euploid abortions, maternal and paternal factors play a more significant role. Optimization of maternal health before pregnancy, correcting structural abnormalities of the uterus, and minimizing exposure to teratogens or infections during early pregnancy can reduce the risks for spontaneous abortion. When optimizing maternal health, special consideration should be given to chronic illnesses such as diabetes and thyroid disease, as well as extremes of weight and use of tobacco products, alcohol, or illicit drugs. Some studies have shown that folic acid supplementation immediately before and during early pregnancy may reduce the risk of spontaneous abortion. It has also been shown in several studies that increasing paternal age is associated with increased risk for pregnancy loss, likely due to increased chromosomal abnormalities. Women should also be educated about reducing the risk of traumatic events and should be screened for risk for intimate partner violence. It is reasonable to recommend preconception counseling to modify these risk factors.

(Mayekar et al., 2020)

(Boiko et al., 2018)

Signs and symptoms

Symptoms of a miscarriage or threatened miscarriage include vaginal bleeding and pain.

- Bleeding may be mild or severe.
- Pain and cramping may be present in the lower abdomen, lower back, buttocks, and genitals.
- Other symptoms associated with a true miscarriage include the passage of blood clots and tissue fragments.

(Ogunyemi et al., 2020)

Diagnosis

The diagnosis is made by history, physical exam, measurement of beta- human chorionic gonadotropin (beta-hCG), and an ultrasound.

A thorough history should be obtained including pregnancy history, medical history, and history of present illness. History of present illness should include when and how symptoms/bleeding began, modifying factors, any treatments trialed up to the point of evaluation, and helping the patient to describe and quantify the bleeding. **(Akerstedt et al., 1978.)**

Transvaginal ultrasound may be used to locate the pregnancy and determine if the fetus is viable. The ultrasound can also help rule out ectopic pregnancy and to evaluate for retained products of conception. A yolk sac is typically seen at 36 days, and a heartbeat is seen on ultrasound at approximately 45 days after the last menstruation **(Axelrod et al., 1984)**.

A beta-hCG level of 1500 lU/mL to 2000 lU/mL is associated with a gestational sac on ultrasound. Beta-hCG doubles in 48 hours in 85% of intrauterine pregnancies. Beta-hCG is usually detectable the first nine to 11 days following ovulation and reaches 200 IU/mL at the expected time of menses.

Rh factor will also determine if Rhogam should be administered to prevent hemolytic disease of the newborn in this pregnancy and subsequent pregnancies. **(Barchas et al., 1989.)**

Hemoglobin and hematocrit levels help monitor the degree of blood loss.

A urinalysis can also be obtained. Urinary tract infection (UTI) has been associated with signs and symptoms of threatened abortion.

During the pelvic exam, suction or cotton swabs may be needed to remove blood and products of conception to allow for better visualization of the cervix. Ringed forceps can also be used to remove tissue that may be protruding from the cervical os. All tissue must be examined to determine if it is a clot or products of conception. Evidence of products of conception protruding from the cervix or within the vagina changes the diagnosis from a threatened abortion to a complete or incomplete abortion. Evaluation of the amount of bleeding/blood loss should be performed through a thorough history, as well as during the pelvic examination.

(Berkowitz, 1981).

Treatment / Management

Alloimmunization prevention by the administration of Rh (D) immunoglobulin should be considered for patients who have vaginal bleeding in the setting of pregnancy in a patient who is Rh-. It has been determined that a 50 mcg dose of immunoglobulin is effective at alloimmunization prevention up to and through the 12th week of gestation, however, it is considered acceptable to give the standard 300 mcg dose due to availability or provider preference.

Patients with a threatened abortion should be managed expectantly without any medical or surgical interventions. However, patients should be given strict return precautions concerning excessive vaginal bleeding, abdominal pain, or fever and patients should be educated on the importance of follow-up. Analgesia can be provided to help relieve discomfort from cramping. NSAIDs should be avoided in the setting of a threatened abortion, as the pregnancy may continue to progress to viability. Follow-up is recommended with serial transvaginal ultrasounds until a viable intrauterine pregnancy is confirmed or until progression to an inevitable, incomplete, or complete abortion occurs. Clinicians can consider serial quantitative beta hCG testing as recommended for a pregnancy of unknown origin to continue to monitor for the viability of the pregnancy, especially in the setting where an intrauterine pregnancy with cardiac activity has not been confirmed by ultrasound. In these cases, it is possible that the pregnancy has not reached the gestational age by which cardiac activity would be expected on ultrasound or it is possible that the pregnancy will not be viable. The patient should be counseled

about the possibility of spontaneous abortion of the pregnancy, as well as the possibility that the pregnancy may continue to progress towards viability. Several trials have shown that progesterone supplementation does not improve outcomes for patients with threatened abortion and progesterone is not currently recommended as treatment or prevention for patients with threatened abortion. Bedrest and other activity restrictions have not been found to be efficacious in the prevention of a threatened abortion progressing to spontaneous abortion and have been shown to increase the risk of other complications including deep vein thrombosis and/or pulmonary embolism and therefore should not be recommended **(Carp, 2018)**. Some providers do prefer to advise patients to avoid strenuous activities and to maintain pelvic rest at least until the cessation of vaginal bleeding. Clinicians should recommend that patients start or continue to take prenatal vitamins with folic acid supplementation. **(Morin et al., 2016)**

Oral manifestation

The storm of hormones which is induced during pregnancy causes changes in the mother's body, and the oral cavity is no exception. Pregnancy gingivitisis a well-recognized entity. The oral changes which are seen in pregnancy include gingivitis, gingival hyperplasia, pyogenic granuloma, and salivary changes. Increased facial pigmentation is also seen. Elevated levels of the circulating oestrogen, which cause an increased capillary permeability, predispose the pregnant women to gingivitis and gingival hyperplasia.

Pregnancy gingivitis usually affects the marginal and the interdental papilla and it is related to the preexisting gingivitis. Good oral hygiene can help in preventing or reducing the severity of the hormone mediated inflammatory oral changes.

Pregnancy does not cause periodontal disease but it does worsen an existing condition **(Gajendra and kumar, 2004)**

Pyogenic granulomas (pregnancy tumours) occur in about 1% to 5% of the pregnant women. Increased angiogenesis, which is caused by sex hormones, coupled with gingival irritation which is caused by local factors such as plaque, is believed to cause pyogenic granuloma. It occurs mainly on the labial aspect of the interdental

papilla. It can happen at any time during a pregnancy, but it is reported to be most common in the first pregnancies, during the first and the second trimesters and it may regress after the child's birth. Although it is uncommon, it is known that the tooth mobility may increase during a late pregnancy. The increased mobility probably results from the changes in the lamina dura, the changes in the attachment apparatus, or from the underlying pathology which is unrelated to the pregnancy. It does not result from the loss of the calcium stores, which is secondary to the pregnancy. If the tooth mobility increases, this problem typically resolves postpartum. Morning sickness is a common problem which is encountered by women, early in their pregnancies. The increased gonadotropins in the first trimester, are associated with nausea and vomiting. Increased levels of progesterone, by a central-acting mechanism, slow the gastric emptying. The gastric acids which are present in the emesis, erode the enamel on the inner surface of the teeth, most commonly the front teeth. This is a concern only in the cases with frequent vomiting, for example, in bulemics and in patients with hyperemesis gravidum . Erosion of the enamel can easily be controlled by advising the patients to rinse their mouths thoroughly after vomiting, with a solution that contains sodium bicarbonate. Sodium bicarbonate neutralizes the acids and it prevents the damage which is caused by the residue which remains on the teeth. Erosion of the teeth which are on the lingual and palatal surfaces of the incisors was mentioned in a case report, but as per our knowledge, there is no clinical study which is available to support this finding **(Koch, 2003)**

It has been said that the mother "loses a tooth for every baby". There is no medical literature to support this statement. The loss of a tooth by a pregnant woman most likely reflects a continuation of her current state of dental health. It is possible that pregnancy gingivitis may sufficiently irritate the gums to make brushing and the routine dental care uncomfortable, and this may hasten the tooth decay. This tooth decay does not occur in most of the patients. The main salivary changes in pregnancy involve its flow, composition, pH and hormone levels. Cross sectional studies have shown a reduced, whole stimulated salivary flow rate in pregnant women, but longitudinal studies have shown that there was no change in the whole stimulated salivary flow rate.The changes in the composition of the saliva include a decrease in the sodium concentration and pH, and an increase in the potassium, protein, and the oestrogen levels.

Checking the salivary oestrogen level has been suggested as a screening test to detect the risk potential for a preterm labour. The salivary oestrogen levels are higher in the women who are destined to have preterm babies than in women who have normal term deliveries. The salivary oestrogen increases the proliferation and desquamation of the oral mucosa and also an increase in the subgingival crevicular fluid levels. The desquamating cells provide a suitable environment for bacterial growth by providing nutrition, thus predisposing the pregnant women to dental caries. **(Chaveli Lopez et al., 2011)**

Dental management guidelines during pregnancy

For the first trimester (1-12 weeks)

During the first trimester, it is recommended that the patients be scheduled to assess their current dental health, to inform them of the changes that they should expect during their pregnancies, and to discuss on how to avoid maternal dental problems that may arise from these changes. It is not recommended that the procedures may be done at this time. The concern about doing procedures during the first trimester is twofold. First, the developing child is at a greatest risk which is posed by teratogens during organogenesis, and second, during the first trimester, it is known that as many as one in five pregnancies undergo spontaneous abortions. Dental procedures which are performed near the time of a spontaneous abortion may be assumed to be the cause, which lead to concerns for both the patient and the practitioner, as to whether this could have been avoided **(sacco et al., 2008)**.

The current recommendations are

- To educate the patients about the maternal oral changes which occur during pregnancy.
- To emphasize strict oral hygiene instructions and thereby, plaque control.
- To limit the dental treatment to a periodontal prophylaxis and emergency treatments only.
- To avoid routine radiographs. They should be used selectively and only whenever they are needed.

For the second trimester (13-24 weeks)

By the second trimester, the organogenesis is complete, and the risk to the foetus is low. The mother has also had time to adjust to her pregnancy, and the foetus has not grown to a potentially uncomfortable size that would make it difficult for the mother to remain still for long periods. The positioning of the pregnant patients is

important, especially during the third trimester. As the uterus expands with the growing foetus and the placenta, it comes to lie directly over the inferior vena cava, the femoral vessels, and the aorta. If the mother is positioned supine for the procedures, the weight of the gravid uterus could apply enough pressure to impede a blood flow through these major vessels and to cause a condition which is called supine hypotension. In this condition, the blood pressure drops secondary to the impeded blood flow, which causes an asyncopal or a near-syncopal episode. This situation is easily remedied by a proper positioning of the patient on her left side and elevating the head of the chair, to avoid compression of the major blood vessels. The dental practitioner should not hesitate to consult the patient's obstetrician, should any question arise about the safety of a procedure, particularly if there are special circumstances which are associated with the pregnancy **(nayak et al., 2012)**

The current recommendations are:

- Oral hygiene, instructions and plaque control.
- Scaling, polishing and curettage may be performed if they are necessary.
- The control of active oral diseases, if any.
- An elective dental care is safe
- Avoid routine radiographs. Use selectively and when they are needed.

Role of salivary cortisol in threating abortion

Human gestation brings about changes in the activity of most endocrine systems in a woman, including the hypthalamic-pituitary-adrenal axis (HPA). These alterations in the HPA axis are important for maintaining an adequate environment for growth and development of the fetus, since an excess or lack of cortisol results in disruption of maternal-fetal homeostasis.

Excess maternal corticoid during pregnancy has been being observed for forty years now, with elevated levels beginning to be detected at around the 12th week of pregnancy**. (Grahame, 2006)**. The difficulty studying alterations in the HPA axis in a pregnant woman is that of establishing a reliable biological marker and a practical diagnostic method which is not influenced by the physiological alterations arising from pregnancy itself. **(patcas et al., 2012)**

The neuroendocrine changes that occur in every pregnancy alter the parameters used by laboratory techniques for dealing with hypercortisolism.Increased levels of

estrogen stimulate the hepatic production of glycocorticoid carrying globulin (GCG).This increase in hepatic GCG, which continues until the 12th day after birth, causes a rise in circulating levels of cortisol linked to the protein and occasions a temporary fall in levels of free cortisol, which, in turn, leads to a reduction in negative feedback to the HPA axis.**(Hashim et al., 2012)** Consequently, levels of the adrenocorticotrophic hormone (ACTH) rise and this stimulates the production of cortisol. The levels of free cortisol are initially normal and then rise during pregnancy and reach maximum levels at the end of the second and third trimesters. Total cortisol and free plasmatic cortisol can reach values that are two or three times higher compared with women who are not pregnant. These high levels of plasmatic cortisol observed in pregnant women are equivalent to those found in Cushing's syndrome.1 the increase in levels of free cortisol during pregnancy also leads to restriction of the action of cortisol during this period. Despite the increase in serum cortisol during pregnancy, the circadian rhythm of the system is preserved, **(capasso et al., 2011)** but it is not known what variation in levels of cortisol is responsible for complications occurring during high-risk pregnancies. Evaluating the levels in normal pregnant women as well as in the high risk group may provide information on these questions **(chaveil lopez et al., 2011)**

To compare the levels of cortisol (cortisolemia refers to the level of cortisol in blood) in women with a high-risk pregnancy compared with those with a low-risk pregnancy, by way of evaluation of levels of cortisol in saliva, using the electrochemical luminescence technique (ECL). METHODS: 38 women aged between 17 and 40 years in the third trimester of pregnancy were divided in two groups: 20 low-risk pregnancies and 18 high-risk ones. Cortisol in saliva was collected at midnight and measured using ECL. The mean levels of cortisol in saliva in the two groups were compared using the Kruskal-Wallis test. RESULTS: the mean systolic and diastolic pressure was normal in both groups. The levels of cortisol in the saliva of women with high-risk pregnancies was significantly higher than those for the low-risk pregnancy group (20.2 (±21, 1) nmol/L vs 11.4(±16.2) nmol/L; p=0.007). CONCLUSIONS: a high risk pregnancy involves higher levels of cortisol than a low-risk one. The levels of cortisol in saliva, as measured using ECL, can be used to identify hypercortisolism in pregnancy.

(Hanshaw et al., 1988)

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