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Are hormones a cause of miscarriage?

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Introduction

Miscarriage (abortion) is defined as the loss of a fetus before it is able to reach Independent of life and growth outside his mother's uterus, which is the difference of its types is a major problem in the field of public health and the inevitable death of the fetus, and despite the different types and causes, the result is either the death of the fetus or in other cases the death of the fetus and the mother together, and the miscarriage may happen one or several times, making up about 20-15% of pregnancies (Sachdeva *et al*., 2011). According to the estimates of the World Health Organization, a quarter of 25% of pregnancies annually end in abortion (WHO, 2018).

The journal "BMC Pregnancy and Childbirth" published a statistic in 2017 that included a large number of women indicating that the percentage of women who underwent an abortion experience during the first trimester of pregnancy may reach to 43% of them. As for the causes of miscarriage, the main cause of miscarriage is often not identified although there are many reasons behind it, and it can be said that a miscarriage during the first trimester of pregnancy is often due to the presence of problems in the fetus itself. Its occurrence after the first trimester; It may be related to the mother's suffering from a specific health problem (Cohain *et al*., 2017). Genetic factors play an important role in miscarriages, at a rate of 5% (Byrne and Ward, 2002), besides, having a pregnant

woman with Diabetes mellitus type II increases the risk of miscarriage and congenital malformations of fetus by 12.3% (Bartha *et al*., 2000).

Many hormones contribute to the regulation of pregnancy, starting with the process of ova formation, fertilization, growth and development of the fetus in all its stages and initiated by the hormone Gonadotropin releasing hormone (GnRH) produced by the hypothalamus, which stimulates the pituitary gland to synthesize and secrete Follicle stimulating hormone (FSH) And luteinizing hormone (LH), and these hormones have a great role in regulating the growth and development of the ovum, ovulation and the fertilization process. Progesterone hormone is one of the most important hormones that work to pregnancy stability and create an appropriate environment for the growth and development of the fetus during all stages of pregnancy (Arck *et al*., 2007), As well as the estrogen hormone just as important as other hormones that contribute to a successful pregnancy, as it plays. This hormone plays an essential role in supporting the secretion and synthesis of thyroid hormones during all stages of pregnancy, especially the first trimester, and even influencing the sex of pregnancy, in addition to the role of Thyroid stimulating hormone (TSH) (Abd and Ismail, 2015), and other hormones.

Pregnancy and Miscarriage

Pregnancy is defined as the period that begins with fertilization of the ovum, its fertilization and implantation of the embryo in the mother's uterus and ends with birth and the exit of the fetus and placenta outside the reproductive system. Pregnancy is a normal functional phenomenon accompanied by an increase in the vital processes and structural metabolism and changes in the levels of many hormones inside the mother's body in a way that aims to create a suitable environment for the fetus inside the uterus and to perpetuate the pregnancy as efficiently as possible, Its duration in women ranges from 280-260 days and an average of 38 weeks. During which pregnant women undergo many internal

metabolic and hormonal changes that affect the efficiency of the body, as the metabolic processes in the female body are directed in a manner that meets the physiological needs of pregnancy and the needs of the fetus for the purpose of growth and development until birth (Guyton and Hall, 2006).

Miscarriage (Abortion) has been defined by the World Health Organization as the process of separation of the fetus from the uterus to the outside and its weight does not exceed half a kilogram or less than 20-24 weeks of pregnancy with no evidence of the continuation of the fetus's life (Cohain *et al*., 2017), or uterus's contents loss (Fetus, Placenta, and Placental Membrane) before the fetus grows in a way that enables it to survive outside the uterus (Kapp *et al*, 2013), Although there is some difference in the details of the occurrence of miscarriage, the final result is the loss of the fetus at an abnormal end of pregnancy that has negative effects on the mother in particular and the family in general. Miscarriage often occurs during the early stages of pregnancy, that is, during the (second trimester) of pregnancy or during the last three months of pregnancy (Third Trimester), and this is no different from premature birth as the fetus is alive in both cases. (Sedgh *et al*., 2012).

Types of Miscarriage

Miscarriage divided in to several types according to (Grimes and Stuart, 2010).

1- Induced Abortion

It occurs when the pregnant mother decides to dispense her pregnancy, either intentionally or for medical reasons, and in both cases the fetus is disposed of surgically by the specialist doctor, then it is called an artificial abortion.

2- Spontaneous Abortion

It occurs when the pregnancy is involuntarily terminated before the fetus reaches a stage that enables it to live outside the uterus, and it accounts for about 10-15% of miscarriages in pregnant women (Homer, 2019) Spontaneous abortion is divided according to the frequency of its occurrence into two types:

First: Sporadic miscarriage: which occurs only once or intermittently several times.

Second: Recurrent spontaneous miscarriage: it may happen three times in a row or more before the twentieth week of pregnancy without a pregnancy that reaches a normal delivary (Grimes and Stuart, 2010).

Causes of abortion occurrence

The occurrence of miscarriage is due to several reasons, some of which are related to the development of the fetus itself, and some related to the pregnant mother, as well as some anatomical and hormonal reasons (Hacker *et al*., 2004). Miscarriage occurs with several causes, including those related to the pregnant mother and those related to the fetus as follows:

A- Related causes of maternal pregnant

1- Anatomically

Pregnancy loss in the second trimester is associated with congenital or acquired anatomical injuries. Which constitutes 15-10% of recurrent spontaneous miscarriages, and represents anomalies of the Muller duct and uterine septa distorting the shape of the uterus, and insufficient capillaries to nourish the fetus inside the uterus due to the small number of anatomical birth infections (Grimes, 2006) As for the inflammatory uterine adhesions which is the cause of severe uterine infections and endometriosis that interference with implantation of the fetus in the endometrium, as well as relaxation of the cervix, all of which are called anatomical injuries (Steinberg, 2011).

2- **Physiologically**

Hormones represent a determining factor for the growth of the fetus inside the uterus and it occupies 10-20% of cases of recurrent spontaneous miscarriage, as the occurrence of any deficiency in the hormone LH as a result of an imbalance In the luteal phase defects, during the formation of the follicle, it leads to spontaneous miscarriage (Kelly, 2014), or low concentration of progesterone (Coomarasamy *et al*., 2020), level of prolactin, and insufficiency of thyroid gland hormones leads to miscarriage in the early stages of pregnancy (Culwell *et al*., 2010) and other causes such as obesity and polycystic ovary syndrome (Kokosar, 2018).

3- Genetically

It represents a chromosomal defect in one or both parents or a defect in the formation of a fertilized ovum during meiosis, forming 2-5% of the causes of miscarriage and 3% among the cases of fetal death in the uterus, as it occurs in the early stages of pregnancy by 70% while in the second trimester of pregnancy 30% (Holmquist and Gilliam, 2008).

4- Septic

Infectious agents represent as a cause of spontaneous abortion and fetal death within the period between the twenty-second week of pregnancy to the twenty-eighth day after birth, it represents 5% of miscarriages arising from a direct impact on the fetus or the placenta, or indirectly from the fever and the accumulation of toxins resulting from it, besides, typhoid fever is considered among the medical problems in pregnant women, it sometimes causes miscarriage or childbirth Deformed children (Halder *et al*., 2015) or affected by the toxoplasmosis parasite (El-sherbini *et al*., 2019).

5- Environmentally

Less than 1% of fetal abnormalities or are connected or related to the mother's exposure to drugs, cancer chemotherapy and other chemicals such as anesthetic gas, formalin, benzene, lead and arsenic, while the aforementioned factors account for approximately 10% of miscarriages, in addition to that, the separation of the fetus from the uterus due to strong trauma, alcohol, exposure to radiation, and smoking lead to abnormalities and miscarriages of fetuses that are no less affected than the previous ones from environmental factors (Thapa *et.al.*, 2006).

6- Immunologically

The incidence of recurrent spontaneous miscarriage increases by 60% when there is an immune defect inside the mother's body that is incompatible with the fetus because the fetus's alloantigens are encoded by the father's genes that provoke humoral immune reactions in the mother leading to fetal loss, pregnancy suppresses the mother's cellular immunity to prevent fetal rejection, and the maternal tissues immune rejection of the developing fetal tissues and the Trophoblast as foreign bodies to the mother's immune system (Kulier *et al.*, 2011).

B- Related causes of fetal

The presence of fetal genetic abnormalities is the reason for the formation of an incomplete fetus inside the mother's uterus, which leads to its miscarriage, and the factors leading to this including:

1- Defect in the protoplasm of the germ cells carrying the genetic traits as a result of a defect in the fertilized ovum, as the presence of basic defects in the fertilized ovum as a result of the failure of male or female gametes leads to incomplete development of embryos (Evans *et al.*, 2013).

2- Chromosomal heterozygous or chromosomal abnormalities as a result of abnormal chromosomal polarity in the group of chromosomes of normal somatic cells, that is, either less than the normal number "Hypodiploid" as in Turner syndrome or higher "Hyperdiploid" as in Down's syndrome, and the result of these changes is miscarriage or the birth of children Genetically disabled (Yinon *et al*, 2013).

Relationship between hormonal parameters and miscarriage

Some hormones are important and necessary factors in regulating pregnancy, and the occurrence of any imbalance in these hormones is considered a cause of miscarriage (Guyton and Hall, 2006). The hormones that are related to miscarriage include the following:

1- Progesterone Hormone

Progesterone hormone is a type of steroid hormone produced from ovarian follicles in the late stages of growth by the influence of the LH hormone, and it is excreted in equal quantities from the ovaries and adrenal cortex and placenta during pregnancy. The progesterone is one of the most important hormones that work to perpetuate pregnancy, and to create an appropriate environment for the growth and development of the fetus during the stages of pregnancy (Al-Alouji, 2008). Have vital functions:

1- Reducing the movement of the ovarian ducts and uterine contractions as a result of reducing the sensitivity of uterine cells to the hormone oxytocin.

2- Works synergistically with the estrogen hormone, on the growth of the uterus and its endometrium, preparing it for the purpose of implantation of the fetus, stimulating the glands in the uterine lining, and increasing its stock of glycogen to maintain the permanence of pregnancy.

3- Inhibition of the activity of the central nervous system and the prevention of ovulation through its combination with estrogen hormone through the mechanism of negative regulation of the hypothalamus.

4- Activating the growth and development of alveoli in the mammary glands.

5- Increasing the insulin hormone directly with the increase in the percentage of glucose in the liver.

The hormone progesterone is one of the most important intermediate compounds that make up steroids in its secreting organs (Guyton and Hall, 2006), and it is considered one of the hormones for the permanence of pregnancy with the estrogen hormone, the first of them is as assistant factor in preparing the endometrium for implantation of the fetus, while the second is a regulator of the physiological activities of the pregnant and the fetus. , low levels of this hormones lead to a spontaneous miscarriage, The corpus luteum remains a stimulator for the production of progesterone until the seventh week of pregnancy when the Trophoblast has acquired the ability of steroid hormones to regulate the physiological activities of the fetus and the mother (support pregnancy), while the lower concentrations of the progesterone after the placenta has separated to spontaneous miscarriage compared to the death of the fetus, which has a lesser effect on the progesterone level in the blood, which indicates the main role of the placenta in the production of progesterone in second and third trimesters of pregnancy (Patton *et al*., 2012). The decrease in hormone concentration in cases of repeated and single miscarriage may come in response to the mother's immune system to reject the fetus (Szekeres-Bartho, 2018) Progesterone is the main hormone to permanence of pregnancy and the use of natural or manufactured progestogens to treat some cases of threatened miscarriage has succeeded in preventing miscarriage and the continuation of pregnancy (Coomarasamy *et al*., 2020).

The sufficient amount of the hormone in the first trimester of pregnancy increases the rate of live births, and it is believed that the reason for this decrease is the effect of some genetic and physiological factors, as well as an increase in some hormones that lead to cause miscarriage, which have a negative effect on the level of the hormone progesterone during pregnancy, such as stress hormones, epinephrine hormone (Nelson, 2003).

The low concentrations of progesterone hormone after fertilization of the ovum and its transformation into an embryo lead to spontaneous abortion, this is due to the inability of the fetus to implant in the endometrium, which leads to an increase in the secretion of the oxytocin and prostaglandin, which lyse the corpus luteum, as a result leads to stop progesterone secretion and increased incidence uterine contractions and miscarriage (Chrestopher *et al*., 2007), as that taking progesterone by pregnant women who still have a corpus luteum with defect or remover before the seventh week was a pregnancy saver (Kulier *et. al*. 2011).

2- Estrogen Hormone

Estradiol (E_2) is the active form of estrogens produced from ovarian follicles under the influence of LH hormone compared to other estrogens produced from different sites of the body besides the ovarian production of estron (E_1) to produce estriol (E_3). The effect of thecal cells hormone is to stimulates the secretion of androgens (Testosterone hormone, Androstenedione hormones), which are transformed in granulosa cells by the action of Aromatases into estrogens (Thomas and Potter, 2013).

Since estrogens are responsible for the formation and development of the female reproductive system, the display of secondary sexual characteristics and the rebuilding of the lining mucosa after the menstrual cycle is also its responsibility, as the vagina, uterus, pituitary, hypothalamus, and mammary glands are the organs in which estrogens show their effectiveness in increasing the

effectiveness of uterus muscles contraction, the movement of the ovum through the fallopian tubes and the growth of the mammary glands, in addition to metabolic functions of estrogens which including:

- Stimulation of adipose tissue to synthesize fat.
- Increase the amount of glycogen in the vagina and endometrium.
- Maintain bone formation.
- Influence on some hormones by stimulating some specialized proteins that are linked to the hormone Thyroxine (T_4) (Guyton and Hall, 2006).

Estrogen is no less important than progesterone in a successful pregnancy, low levels of the two hormones lead to a spontaneous abortion (Patton *et al*., 2012).

The importance of the role that estrogen plays during the first and third stages of pregnancy lies through its negative effect in the production and secretion of GnRH hormones from the hypothalamus and FSH from the pituitary gland to prevent the formation of new ova in the first stage of pregnancy (Klein *et al*., 1996), as well as for estrogen great importance in preparing the uterine environment at the beginning of pregnancy in cooperation with the progesterone in addition to its role in increasing the concentrations of transporting proteins for Triiodothyronine (T_3) and T_4, which results in an increase in the concentrations of these hormones during this stage due to their great and sensitive importance in the development of the fetus and the success of pregnancy (Tunancyija , 2011).

3- Follicle stimulating hormone and Luteinizing hormone

The hormones LH and FSH are secreted by the anterior lobe of the pituitary gland during the ovarian cycle, LH hormone is also called ovulation hormone, it is responsible for the detonation of the follicle cover and the release of the ovum from the ovary, i.e. ovulation. Both hormones change their secretion during the ovarian menstrual cycle; they rise and fall from day to day depending on the

growth of the follicle, its bursting then the formation of the corpus luteum. Therefore, they have great benefit from their analysis to diagnose hormonal disorders and ovulation, and this is especially true for the hormone LH, as for the FSH hormone, its high and low indications are only used to diagnose one of two things:

1- Insufficiency of the pituitary gland: FSH decreases greatly, leading to severe ovulation impairment and early menopause.

2- The expected or early menopause: where ovulation is severely weakened, which leads to a high hormone level, trying to stimulate the tired and out-of-function ovaries to secrete more ova and hormones. An FSH rise of more than 20 IU / liter is a sign of entering the menopause, and the weaker the ovarian function and the older the ovarian insufficiency, the more high the hormone level (Guyton and Hall, 2006).

The ovarian hormones estrogen and progesterone indirectly affect the secretion of LH from the anterior lobe of the pituitary gland through the positive and negative feedback mechanism, depending on their concentration in the blood. LH secretion is inhibited by high concentrations of estrogen and progesterone through the negative feedback mechanism (Warren and Stiehf, 1999). Likewise, the imbalance in the corpus luteum and the lack of the hormone LH, thus a low concentration of progesterone, leads to spontaneous abortion (Naji and Taher, 2016) because the LH hormone stimulates the corpus luteum to secrete the progesterone, which has a major role in maintaining pregnancy in early stages until the placenta grows (Blumenfeld and Ritter, 2006).

The decrease in the concentration of LH and progesterone increases the concentration of FSH in the blood. As the ovarian hormones (estrogen and progesterone) affect the secretion of this hormone in pregnant women from the anterior lobe of the pituitary gland through positive and negative feedback effects

depend on their concentration in the blood, which leads to its increase during pregnancy to abortion (Klein *et al*., 2004).

4- Thyroid gland Hormones

The Thyroid gland responsible for synthesis and secretion of the hormones T_3 and T_4. T_3, which contains three atoms of iodine, and the thyroxine hormone, which contains four atoms of iodine, so iodine is an essential and necessary component for the production of thyroid hormones, which is what the gland gets from the food we eat. The thyroid gland produces thyroxine in a greater amount than the thyroid hormone, so thyroxine can be converted into T_3 in many tissues by an enzyme called deiodinase, and among the functions of thyroid hormones are the following:

- Regulating the body's metabolism and energy production.
- Regulating the amount of oxygen consumed by cells.
- Regulating the functions of: the brain, the heart, the kidneys, the skin, the hair, the eyes, the intestine, and the muscles.
- Regulating body temperature. Regulating brain and nerve functions, and regulating their development.
- Regulating human growth.

Thyroid hormones as the other hormones; most important in the process of metabolism and building of tissue of fetal organs from the beginning of pregnancy until birth, and it is also noticed that during all stages of pregnancy an increase in the size and activity of the thyroid gland of the pregnant mother and an increase in its secretion of the hormones T_3 and T_4, and it was found that the role of its hormones is of great importance in the development of the brain and other organs of the fetus and its deficiency during pregnancy leads to mental retardation in the newborn, with a decrease in the growth of the newborns and congenital

malformations in them, or it may lead to miscarriage in the early stages of pregnancy (Culwell *et at*, 2010).

The fetus depends during the first stage on the rise of the estrogen hormone to promote high concentrations of the hormone (T_4) Thyroxine which synthesized by the pregnant mother, as it has a direct effect on the production of proteins by liver which transport or carrying the hormones T_4 and T_3. And that any deficiency in the function of the thyroid gland without attention to it, exposes the fetus to danger through its effect on the development of the nervous system development of the newborn after birth, and there is a hypothesis that says that the first stage of pregnancy should increase the levels of the hormone T_4 regardless of the level of TSH that has a positive relationship with the development of the cerebral cortex of the fetus, T_4 as it is considered the strategic storage of T_3 hormone (Lazarus, 2002).

TSH concentration increases during the first and second stages of pregnancy compared to the third stage, and it is believed that the reason for this is due to the high concentrations of the Human Chorionic Gonadotropin (hCG) during the first stage of pregnancy, which has a positive role in raising the level of this hormone. As this hormone considered as most effective factors responsible for causing hyperthyroidism during the first three months of pregnancy, this condition causes a decrease in the weight of the pregnant mother by about 5% of the body weight for weeks 6-9 of the pregnancy. The T_3 hormone has an important and sensitive role in the developmental processes of the fetus and placenta growth during this stage (Hershman, 2008).

5- Prolactin Hormone

It is called the hormone that stimulates the growth of the mammary glands, which is an amino hormone. In the anterior lobe of the pituitary gland, there is a group of cells called Lactotrophs. Their number and size varies according to the

physiological condition of women, as they increase during pregnancy and are responsible for the production of the milk hormone (Grattan *et al*, 2007) The prolactin hormone, in cooperation with the hormone LH, activates the corpus luteum in the ovaries, and then it is known as the hormone that nourishes the yellow body to maintain it during pregnancy, so it becomes one of the hormones that nourish the gonads (Al-Alouji, 2008).

The increase in the level of estrogen in the blood is accompanied by a positive increase in the level of prolactin in many women, which indicates the role of estrogens in inducing prolactin to release and increase its concentration in the blood, as estrogens stimulate various mechanisms of milk hormone secretion, including the inhibition of dopamine synthesis in the hypothalamus and reducing the number of dopamine receptors to stimulate the synthesis of the prolactin through its effect on the secretory cells of it directly and its interference in the mechanism of stimulating the mitotic susceptibility of the cells secreting the prolactin hormone (Tam *et al*., 2010),

While there are other factors that stimulate prolactin hormone, but they are not permanently modified, such as TRH, which stimulates the production of prolactin hormone when injected into the human vein (Larsen and Grattan, 2012), and when the pituitary gland is affected by some tumors, it is inhibited dopamine due to pressure on the blood vessels between the pituitary gland and the hypothalamus, resulting in hyperprolactinemia, which causes a lack of menstruation in women (Zinger *et al*, 2003).

6- Testosterone Hormone

25% of testosterone is derived from the ovaries, 25% from the adrenal cortex, and 50% from the primary androgen conversion (Pinola, 2016). A change in testosterone concentrations is not observed during the three stages of

pregnancy. This is due to the fact that the androgenic hormones during pregnancy are converted into estrogen in the presence of the aromatase enzyme.

It was found that the high level of this hormone above the normal limits leads to suppression of the production of thyroid hormones, which results from a decrease in the levels of the metabolism process and a weakness in the growth and development of the fetus, thus deforming the fetus. The high level of testosterone hormone during the first stage of pregnancy leads to an increase in the brain weight and thickness of the cerebral cortex in the fetus (Carlsen *et al*., 2006).

7- Activin Hormone

It is a complex glycoprotein hormone, produced by the placenta and fetal fluid, and it has a role in the birth of the fetus, and the placenta is the main source of this hormone. The activin hormone increases the formation and stimulation of FSH secretion and participates in the regulation of the uterine cycle, as well as its role in cell proliferation, differentiation, apoptosis, metabolism, homeostasis, immune response, and wound repair (Florio *et al*., 2004). It has been found that the role of the activin hormone is to stimulate the secretion of the GnRH, FSH and the oxytocin hormone, which has an important role in the abortion process (Lamba *et al*., 2006). Measuring the level of the activin hormone at the beginning of pregnancy is useful in diagnosing the deficiency of the trophoblastic function and also helps in controlling the problems of early pregnancy in the first trimester of pregnancy in women who experience bleeding during pregnancy that leads to a fetus threatened with miscarriage (Naji and Taher, 2016). Muttukrisha *et al* (2000) indicated that the concentration of the activin hormone increases in the case of complete abortion and removal of the placenta, as the maternal hormone concentrations after removing the fetal placenta gradually begin to decrease within the first hours, and this explains that the placenta is the main source of the this hormone.

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