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Predictable correlation between ACTH and Cortisol in Women with Aborted Pregnancies and its Association with Cytomegalovirus (CMV) Infection

[1] Hawraa Ahmed Ali, [2] Mohammed Sabri Abdul-Razzag, [3] Milal Muhammad Al-Jeborry

[1] Department of Pharmacy Techniques, Babylon Technical Institute, Al-Furat Al-Awsat Technical University31001, Kufa, Al-Najaf, Iraq. hawraa.ahmed2310@gmail.com

[2] Department of Microbiology, College of Medicine, Babylon University, Hilla, Iraq. dr.mohammedsabri1964@gmail.com

[3] Department of Surgery, College of Medicine, Babylon University, Hilla, Iraq. melal.mohamed@uobabylon.edu.iq.com

*Corresponding author email. hawraa.ahmed2310@gmail.com

العلاقة المتوقعة بين الكورتيزول وهرمون القشرية الكظرية لدى النساء ذوات الحمل المجهض وارتباطه بعدوى فايروس المضخم للخلايا

حوراء احمد علي [1], محمد صبري عبد الرزاق [2], ملال محمد الجبوري [3]

[1] جامعة الفرات الاوسط التقنية , المعهد التقني بابل, تقنيات الصيدلة hawraa.ahmed2310@gmail.com

[2] جامعة بابل , كلية الطب, الاحياء المجهرية dr.mohammedsabri1964@gmail.com

[3] جامعة بابل , كلية الطب , قسم نسائية والتوليد melal.mohamed@uobabylon.edu.iq.com

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ABSTRACT

Background: Abortion is a spontaneous termination of pregnancy with various causes, including infections like cytomegalovirus (CMV). Cytomegalovirus is a common viral infection that can affect various organs and systems in the body. **Aim of study:** This research aims to investigate the concertation level of Cortisol and ACTH hormones that may play a role in crucial processes during pregnancy.

Materials and methods: This study conducted at Maternity and Children's Hospital in Hilla from November 2023 to March 2024 focused on 250 women who had undergone abortions. Participants were divided into two groups: 200 women with abortions (Positive Group) and 50 healthy married women (Control Group).

Results: we found 60 Cytomegalovirus were positively obtained from women with abortion, The serological diagnosis for CMV-positive samples found that 6 samples were seropositive to CMV IgM, 14 samples were seropositive for both IgM & IgG, and 40 (samples were seropositive for CMV IgG only. The study investigated the concertation hormone levels of Cortisol and ACTH in women who had experienced abortions with cytomegalovirus (CMV) infection compared to a Control group of healthy married women. The results showed that the patient group had significantly lower cortisol levels, at a mean value of 42.1158. On the other High levels are present in the blood of women with CMV. There is a **:**hand,(ACTH) of (78.1468).**conclusion** decreased level of Cortisol in women miscarriage with CMV infection which is statically significant.

Keywords: Abortion; CMV; Cortisol; Adrenocorticotropic (ACTH) hormones

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INTRODUCTION

Abortion, the spontaneous termination of a pregnancy before the fetus reaches viability, can have various underlying causes, including infections[1]. Among these infections, cytomegalovirus (CMV) has been recognized as a potential contributor to adverse pregnancy outcomes[2]. Cytomegalovirus can cause disease infection, which belongs to the herpes virus family. CMV is a ubiquitous virus, meaning it is found in people worldwide and can infect individuals of all ages. Most people who become infected with CMV do not experience any symptoms or only have mild symptoms. However, it can be a serious concern for certain groups of people, especially those with weakened immune systems [3]. Many diseases may be caused by this virus, but the most common syndrome caused by this virus is its effectivity on a pregnant woman and causes abortion, Several contradictory studies that describe the relationship between Human Cytomegalovirus infection and pregnancy loss demonstrate that HCMV can cause miscarriage or stillbirth, Pregnancy-related HCMV susceptibility rates are well documented, and among women of childbearing age[1].CMV is a common herpesvirus that can be transmitted vertically from mother to fetus during pregnancy, leading to congenital CMV infection and associated complications[4]. Cytomegalovirus belongs to the family Herpesviridae, specifically the subfamily Betaherpesvirinae. The family Herpesviridae consists of a large group of DNA viruses that infect various animal species, including humans. This family is further divided into three subfamilies: Alphaherpesvirinae, Betaherpesvirinae, and Gammaherpesvirinae[5]. After the primary infection with cytomegalovirus (CMV), the virus can indeed establish a lifelong latent infection in the body. During latency, CMV remains dormant or inactive within certain cells, particularly white blood cells (specifically, monocytes and T cells). The virus's ability to remain latent in the host's cells is a characteristic of herpes viruses, to which CMV belongs. However, the virus can reactivate under various circumstances, which can lead to symptomatic infections, particularly in individuals with weakened or compromised immune systems. Reactivation of CMV can occur in People with weakened immune systems, such as those with HIV/AIDS, individuals receiving immunosuppressive medications after organ transplantation, or individuals undergoing chemotherapy, who are at a higher risk of CMV reactivation. The virus can become active when the immune system's ability to control it is compromised, Stress, illness, and other factors that weaken the immune system's function can trigger CMV reactivation [6]. Also, Pregnant

women, particularly those who have not been previously exposed to CMV, can experience primary infection during pregnancy. CMV is a double-strand DNA virus that affects people of all ages and is a member of the herpesviruses Like other herpesviruses, CMV remains dormant within the host after recovery of initial infection. Viral reactivation occurs during the compromise of the immune system with immunosuppression [7].

Cytomegalovirus (CMV) is a common viral infection that can affect various organs and systems in the body. One area of interest in CMV research is its potential impact on hormone levels, particularly cortisol and ACTH. Cortisol is a steroid hormone produced by the adrenal glands, which are located on top of the kidneys. It is involved in a wide range of physiological processes, including metabolism, immune response, and stress regulation. ACTH, on the other hand, is a hormone produced by the pituitary gland in the brain, and it stimulates the production and release of cortisol from the adrenal glands [5]. However, it is important to note that cortisol levels can fluctuate throughout the day, with higher levels in the morning and lower levels in the evening. Therefore, the timing of the blood test may influence the results, and multiple samples may be necessary to understand the cortisol pattern comprehensively [8]. In addition to cortisol, ACTH levels can provide valuable information about the functioning of the adrenal glands. High levels of ACTH may suggest an overactive adrenal gland, while low levels may indicate an underactive gland [9]. The potential impact of cytomegalovirus (CMV) infection on hormone levels and hormone disturbances, particularly in the context of women experiencing miscarriage due to CMV infections, is an area of ongoing research. CMV infection can interfere with hormonal balance, particularly affecting hormones essential for maintaining pregnancy, such as progesterone and estrogen. The virus can destroy the process of hormones which causes hormonal imbalance which can lead to miscarriage and poor uterine .for the growing fetus.[26]

CMV is known for its ability to establish latent infections and can cause a wide range of health issues, including congenital infections. Still, its direct influence on hormonal regulation is not fully understood.

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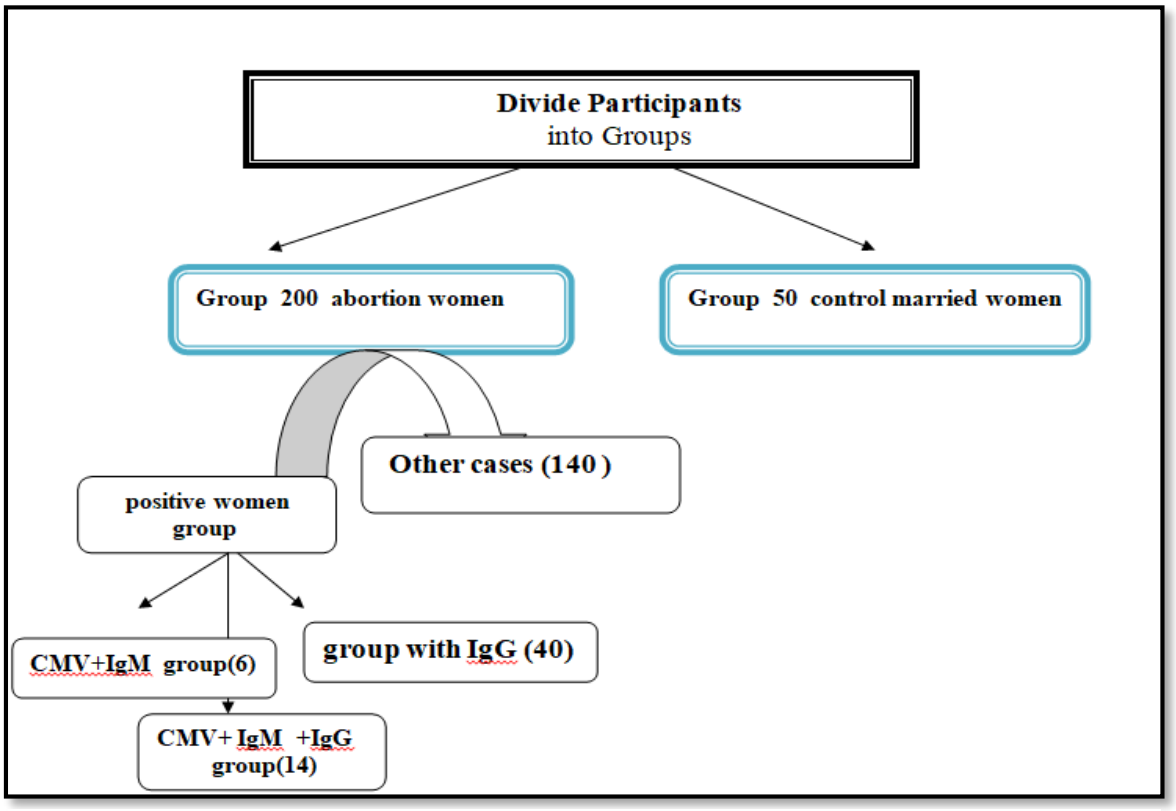
METHOD AND MATERIAL

Study Design and blood collection:

The study conducted at Maternity and Children's Hospital in Hilla from November 2023 to March 2024 focused on women who had undergone abortions. The total number of participants in the study was 250. The participants were divided into two main groups: Positive Women Group, which comprised 200 participants. Control Group: The control group included 50 healthy married women obtained from clinical sources. to collect the blood samples, strict aseptic conditions were maintained. Approximately five milliliters of blood were collected from each participant through vein puncture after the skin was properly cleaned. After collection, 3ml from the blood samples were allowed to clot by incubating them. Subsequently, the samples were centrifuged at 3000 rpm for five minutes. This centrifugation process separated the serum from other blood components and was then carefully collected in sterile containers, The serum was collected in sterile containers and stored at (-20°C) until tested. 2ml of which was kept in an EDTA tube for plasma ACTH after centrifugation Figure 1" provided in includes any information from that figure in the summary.



prevalence of CMV among collected samples Figure (1):

Detection of CMV IgM and IgG:

Serological Detection for Cytomegalovirus (CMV) IgM, IgG [10]: All serum samples have estimated the concentration of levels for virus-specific antibodies Anti-IgG & IgM markers using Vidus Kits for CMV IgM, IgG was used (Biomereux, Company France).

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Estimation of Cortisol Hormone, and Adrenocorticotrophic Hormone (ACTH) by VIDAS.

VIDAS (Vitek Immuno Diagnostic Assay System) is an automated immunoassay system developed by bioMérieux, a leading global in vitro diagnostics company.

The principle of VIDAS is based on the enzyme-linked fluorescent assay (ELFA) technology, which is varied from enzyme-linked immunosorbent assay (ELISA). The process of the VIDAS system involved:

The interpretation of serum cortisol results obtained through the VIDAS Cortisol assay is based on the reference ranges or cutoff values established by the laboratory or the manufacturer of the assay. The reference ranges may vary depending on factors such as the time of day when the sample was collected, and the population being studied

- For the morning cortisol levels, the expected range is 54.94 ng/mL to 287.56 ng/mL. Most healthy individuals' morning cortisol levels will be within this range.
- For the afternoon cortisol levels, the expected range is 24.61 ng/mL to 171.52 ng/mL, reflecting the range where most healthy individuals' afternoon cortisol levels are expected to fall.

The results for ACTH using the VIDAS assay. Based on the reference range for ACTH levels using the VIDAS method is: Reference Range: 6.0 - 76.0 pg/mL. This means that in a healthy population, the typical ACTH levels fall within this range. Any ACTH results below 6.0 pg/mL or above 76.0 pg/mL would be considered outside the normal range.

So, The VIDAS system's automation, speed, and precision make it a valuable tool in clinical laboratories for diagnosing infectious diseases and monitoring patient health. It is widely used worldwide and has contributed significantly to the field of in vitro diagnostics.

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RESULT AND DISCUSSION

Human Cytomegalovirus Seroprevalences in Women with Abortion

The serological diagnosis for CMV seropositive patients found 60(30%) were positively obtained from women with abortion, divided into 6 (10%) samples that were seropositive to IgM, 14 (23.3%) samples were seropositive for both IgM & IgG, and 40 (66.7%) samples were seropositive for IgG, as shown in figure (2)

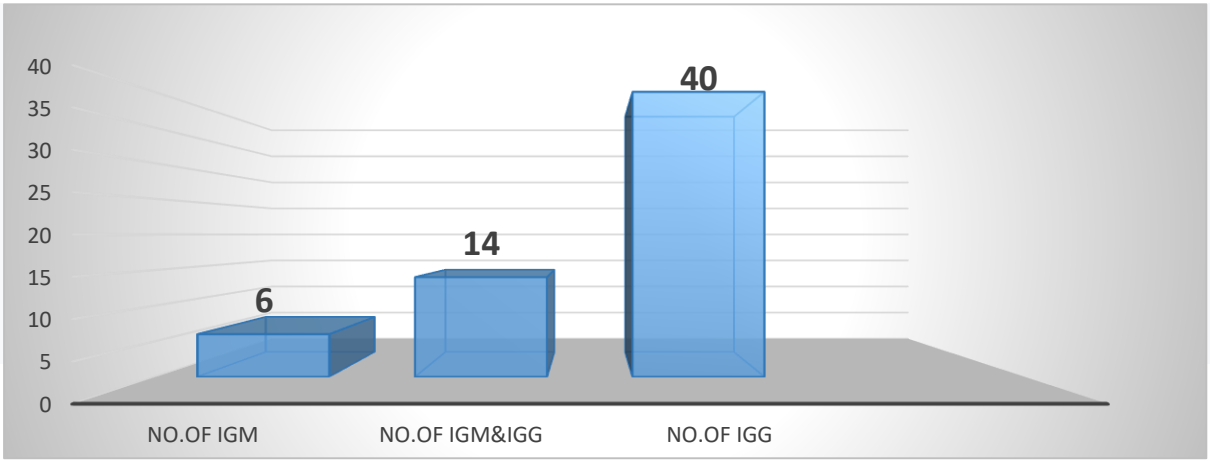

Figure (2): serological analysis of seropositive patients with CMV.

Cortisol and Adrenocorticotropic Levels in Women Patients with CMV Infection

A study included serum cortisol and plasma ACTH levels estimation between patients and a control group. The results showed that the patient group had significantly lower cortisol levels, at a mean value of 42.1158, compared to the control group average of 114.2062. On the other hand, women who had miscarriages had higher levels of Plasma Adrenocorticotropic hormone (ACTH) compared to the control group, with a difference of (78.1468, *P* 0.001) compared to the control group's 45.18. These findings are illustrated in Figures (3) and (4)

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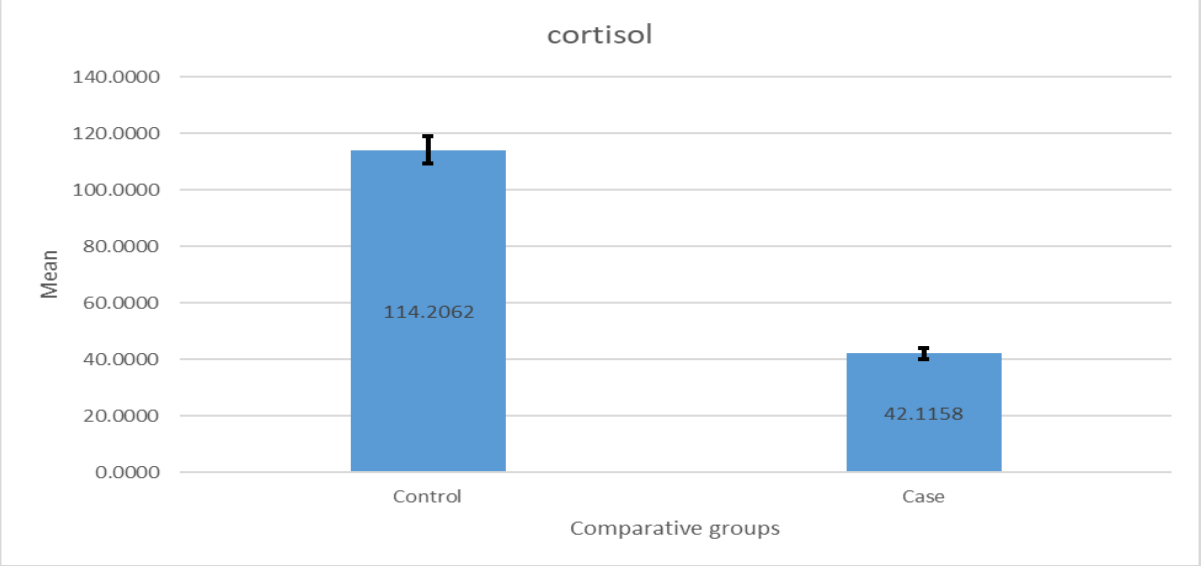

Figure (3) Mean value of Cortisol in miscarriage women patients with CMV and control

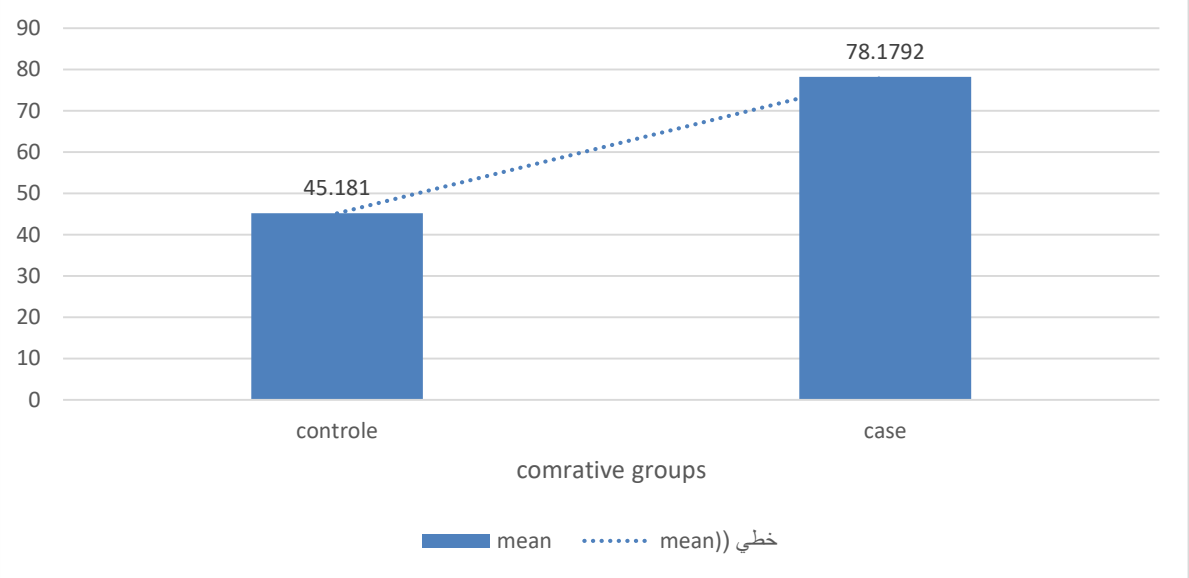

Figure (4) mean value of ACTH in miscarriage women patients with CMV and control

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DISCUSSION

Cytomegalovirus (CMV) is a common virus belonging to the herpesvirus family [11]. Infections with CMV are typically asymptomatic or cause mild flu-like symptoms in healthy individuals [12]. However, CMV can pose significant risks during pregnancy, especially if a woman becomes infected for the first time (primary infection) or experiences reactivation of a latent CMV infection [13]. In this study, the prevalence of Cytomegalovirus (CMV) infection was positive in 60 (30 %), This result is similar to that reported in other research findings (32.78%) [14]. But disagree with the lower prevalence in the previous investigation reported in Iraq 56 % [15]. CMV infection during pregnancy can have significant implications, including congenital CMV infection, which may lead to various health issues in the newborn, such as hearing loss and developmental delays [16]. CMV can be related during pregnancy, labor, and childbirth which is at a high risk to pregnant women [17]. Quality measures and procedures can help minimize, prevent, and promote healthy pregnancy.

The relationship between cytomegalovirus (CMV) infection and cortisol and ACTH levels involves a complex mechanism. CMV infection can stimulate the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6), which can then affect the hypothalamic-pituitary- When CMV adrenal (HPA) axis, the regulatory system that controls cortisol production. infects the body, it triggers an immune response characterized by the release of various inflammatory molecules. This immune response can lead to the activation of the HPA axis. The hypothalamus releases corticotropin-releasing hormone (CRH), which then stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates the adrenal glands to produce and release cortisol [18].

High cortisol formation fights, protects and prevents the body from improper functioning [19].

In some cases, CMV infection can lead to prolonged HPA axis activation, resulting in chronically elevated cortisol levels. This prolonged exposure to high cortisol levels can have negative effects on the immune system and overall health. It may impair immune function, increase susceptibility to other infections, and contribute to the development of certain health conditions, such as metabolic disorders and mood disturbance [20].

Weak immune systems of individuals have a higher risk factor in the body in an advanced stage of CMV infection [21]. These hormones are not previously studied to show their role in CMV infections as biomarkers but they need ongoing studies to show their role at genetic levels. The relationship between CMV and cortisol/ACTH is complex and needs to be fully understood. A study [22]. found that. the lungs, pancreas, kidneys, and liver are the organs most affected by CMV, also, the adrenal glands are common organs affected by CMV.

The virus can directly infect and damage the adrenal glands, impairing cortisol synthesis. Additionally, CMV infection can also suppress the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for regulating cortisol production. The exact mechanisms by which CMV affects the HPA axis are not fully understood but may involve viral proteins interfering with signaling pathways in cortisol synthesis [23]. CMV infection determines the overall health effect on an individual depending on their body's well-being [20].

It is unclear how CMV affects the adrenal gland, but some believe it might be an infection source. The virus seems to deplete the gland's resources and increase the likelihood of adrenal insufficiency, but symptoms only arise when over 90% of the gland has been damaged. As a result, functional issues with the gland can go unnoticed until complete adrenal insufficiency sets in, which can be life-threatening [24]. If a person experiences chronic or persistent CMV infection, it may cause adrenal insufficiency. This is a condition where the body does not produce enough cortisol. The virus can damage the adrenal glands or trigger autoimmune destruction of the adrenal tissue, leading to this condition. Even if the person is stimulated by high levels of ACTH, the adrenal glands may still be unable to produce enough cortisol [25].

Although this study included two hormones to show their relationships to CMV infection and miscarriage, it still requires further investigation to show whether cortisol levels are affected due to CMV infections or whether there is variation in this value due to the time of samples obtaining.

The relationship between CMV infection and ACTH levels is still being studied, and further research is needed to fully understand the mechanisms involved.

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CONCLUSION

Cytomegalovirus is found in some women with miscarriage when IgM or IgG and IgM are high. High levels of ACTH are present in the blood of women with CMV. There is a decreased level of Cortisol in women's miscarriage with CMV infection which is statically significant.

Conflict of interests.

There is no conflict interest

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الخلاصة

الإجهاض هو إنهاء عفوي للحمل لأسباب مختلفة، بما في ذلك العدوى مثل الفيروس المضخم للخلايا (CMV). الفيروس المضخم للخلايا هو عدوى فيروسية شائعة يمكن أن تؤثر على أعضاء وأنظمة مختلفة في الجسم. هدف الدراسة: يهدف هذا البحث إلى دراسة مستوى تناسق هرمونات الكورتيزول والـ ACTH التي قد تلعب دورًا في العمليات الحاسمة أثناء الحمل.

المواد والطرق: ركزت هذه الدراسة التي أجريت في مستشفى الولادة والأطفال في الحلة من تشرين الثاني 2023 إلى آذار 2024 على 250 امرأة خضعن لعمليات إجهاض. تم تقسيم المشاركين إلى مجموعتين: 200 امرأة تعرضت للإجهاض (المجموعة الإيجابية) و50 امرأة متزوجة تتمتع بصحة جيدة (المجموعة الضابطة).

النتائج: وجدنا 60 فيروسًا مضخمًا للخلايا تم الحصول عليها بشكل إيجابي من النساء اللاتي تعرضن للإجهاض، وجد التشخيص المصلي للعينات الإيجابية للـ CMV أن 6 عينات كانت إيجابية مصليًا لـ CMV IgM، و 14 عينة كانت إيجابية مصليًا لكل من IgM و IgG، و 40 (كانت العينات إيجابية مصليًا لـ CMV). بحثت الدراسة في مستويات هرمون الكورتيزول والـ ACTH لدى النساء اللاتي تعرضن للإجهاض بعدوى الفيروس المضخم للخلايا (CMV) مقارنة بمجموعة مراقبة من النساء المتزوجات الأصحاء. وأظهرت النتائج أن مجموعة المريضات كانت لديها مستويات أقل بكثير من الكورتيزول متوسط قيمة (42.1158) من ناحية أخرى، (ACTH) من (78.1468).

الاستنتاج: توجد مستويات عالية في دم النساء المصابات بفيروس CMV، هناك انخفاض في مستوى الكورتيزول لدى النساء اللواتي أجهضن بعدوى فيروس CMV وهو أمر ذو دلالة إحصائية

الكلمات المفتاحية: الإجهاض، فايروس المضخم للخلايا، الكورتيزول، وهرمونات قشر الكظر

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