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Evaluation of Cytomegalovirus Infection and Interleukin-33 Levels in Women with Recurrent Pregnancy Loss

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Abstract

Background

Recurrent pregnancy loss determine by the "American Society for Reproductive Medicine" and the "European Society of Human Reproduction and Embryology", is defined as two or three clinically identifiable failed pregnancies before twenty to twenty-four weeks of gestation, as confirmed by histopathologic examination or ultrasound. The cytomegalovirus is a member of the Herpesviridae family's Betaherpesvirinae subfamily. It is a common virus that is known to cause congenital infections in infants and in people with weakened immune systems as pregnant. Interleukin 33 (IL-33) a cytokine, is a member of the Interleukin 1 family. bind to the special ST2 receptor.

The aim of study

To determine the unbalanced inflammatory factors such as interleukins 33 (IL-33) and cytomegalovirus infections can be an important factor in recurrent pregnancy loss.

Methods & materials

This study's case-control methodology included 60 Recurent pregnancy loss as case group and 60 healthy controls with successful delivery. IL-33 measure & CMV IgM and IgG from serum blood samples using ELISA technic method.

Results

The obtained results showed that measure of IL-33 in the control was significantly more than case ($p = 0.001$). cytomegalovirus antibodies in the control were significantly more than case (IgM) ($p = 0.01848$). & (IgG) ($p = 0.00001$) , BMI and Age non-significant to link with RPL .

Conclusion

Generally, we showed that the BMI & Age no important role but IL- 33 level and cytomegalovirus infections play an important role in RPL.

تقييم الإصابة بفيروس السيتوميجالو (CMV) ومستويات الإنترلوكين-33 لدى النساء المصابات بالإجهاض المتكرر

محمد كاظم مطشر , تغريد فاضل المحبوبي , احمد موسى عيسى

الملخص

المقدمة

تُعرّف الإجهاضات المتكررة، وفقًا للجمعية الأمريكية للطب التناسلي والجمعية الأوروبية للتكاثر البشري وعلم الأجنة، بأنها فشل حدوث حمل سريري يمكن التحقق منه مرتين أو ثلاث مرات قبل بلوغ فترة الحمل من 20 إلى 24 أسبوعًا، وذلك كما تؤكده الفحوصات النسيجية أو التصوير بالأمواج فوق الصوتية. يُعد الفيروس المضخم للخلايا (Cytomegalovirus) من فيروسات عائلة الهربس (Herpesviridae) وتحديدًا من فصيلة الـBetaherpesvirinae ، وهو فيروس شائع ومعروف بتسببه في إصابات خلقية لدى الأجنة، بالإضافة إلى تأثيره في الأشخاص ذوي المناعة الضعيفة، مثل النساء الحوامل. يُعتبر الإنترلوكين 33 (IL-33) من السيتوكينات التابعة لعائلة الإنترلوكين 1، ويرتبط بالمستقبِل النوعي.ST2

هدف الدراسة

تهدف هذه الدراسة إلى تحديد ما إذا كانت العوامل الالتهابية غير المتوازنة مثل الإنترلوكين 33 (IL-33) والعدوى بفيروس المضخم للخلايا (CMV) تلعب دورًا مهمًا في حدوث الإجهاضات المتكررة.

العينات وطرق العمل

أُستخدم في هذه الدراسة تصميم الحالة–الشاهد، حيث شملت 60 امرأة تعاني من الإجهاض المتكرر كمجموعة الحالات، و60 امرأة ذوات حمل ناجح كمجموعة ضابطة. تم قياس مستويات IL-33 والأجسام المضادة IgM و IgGلفيروس CMV في عينات الدم المصلية باستخدام تقنية الإليزا.(ELISA)

النتائج

أظهرت النتائج أن مستوى IL-33 كان أعلى بشكل ملحوظ في مجموعة الضوابط مقارنةً بمجموعة الحالات .($p = 0.001$) كما كانت الأجسام المضادة لفيروس CMV (IgM و IgG)أعلى بشكل ملحوظ لدى المجموعة الضابطة مقارنةً بمجموعة الحالات، حيث بلغت القيم الاحتمالية ($p = 0.01848$) و ($p = 0.00001$)على التوالي. في المقابل، لم يظهر كل من مؤشر كتلة الجسم (BMI) والعمر ارتباطًا ذا دلالة إحصائية مع حالات الإجهاض المتكرر.

الاستنتاج

بشكل عام، تُظهر نتائج هذه الدراسة أن كلًّا من العمر ومؤشر كتلة الجسم لا يلعبان دورًا مهمًا في حدوث الإجهاضات المتكررة، في حين أن انخفاض مستويات IL-33 والعدوى بفيروس CMV يُحتمل أن يكون لهما دور بارز في هذه الظاهرة.

1. Introduction

A multifactorial event known as recurrent pregnancy loss (RPL) occurs when two or three consecutive abortions occur before 20 weeks of gestation. One to five percent of women of reproductive age suffer from RPL because several causes such as a severe reproductive issue (Turesheva et al., 2023). Haematological, anatomical, chromosomal ، genetic, and endocrinological variables all contribute to the pathogenicity of RPL, a diverse disorder. Environmental variables of RPL also include exposure to ethylene oxide and lead. Additionally, immunological and infectious factors. also, by incorrect medication use (Pei et al., 2019; Turesheva et al., 2023). Interleukin 33 (IL-33) Known as IL-1F1-IL-1F11, it is a new cytokine that is a member of the 11-member IL-1 family. IL-33 is liganded by the orphan receptor T1/ST2 (IL-1RL1) (Cayrol & Girard, 2018).

A healthy pregnancy is linked to the balance of Th1 & Th2 cytokines. Furthermore, the physiological development of the human foetus is influenced by the decrease of Th1 cytokines throughout pregnancy (Ahmadi et al., 2017; Wang et al., 2020). Human cytokine production is regulated by genetic background. The immune system and inflammatory processes are both significantly regulated by this cytokine, endothelial cells produce IL-33, which is crucial for Th2 and mast cell activation. Additionally, it belongs to the IL-1 family and is essential for immunological responses as well as a number of physiological and pathological processes, including tissue homeostasis, autoimmune disorders, and cancer (Cayrol, 2022; Cayrol & Girard, 2022; Molofsky et al., 2015). Human cytomegalovirus It is Part of the Herpesviridae family's Betaherpesvirinae, Direct or indirect contact with bodily fluids, including saliva, urine, cervical or vaginal secretions, semen, breast milk, or blood, is the main way that the infection is spread. A pregnancy can be greatly impacted by the cytomegalovirus (CMV), which may result in unfavourable results, such as abortion. Significant inflammation and cellular damage can result from placental cell infection by the cytomegalovirus (CMV). Reduced effectiveness in the transport of vital nutrients and oxygen from the mother to the fetus results from this infection's disruption of the placenta's normal design and function. A miscarriage is more likely as a result of the ensuing placental insufficiency, which can seriously impair fatal growth and development. Further raising the possibility of spontaneous abortion is the possibility that CMV-induced placental damage may hinder the generation of vital hormones required to sustain pregnancy. (Lindholm & O'Keefe, 2019). It is a prevalent virus that can cause serious infections in adults with compromised immune systems and congenital illnesses in neonates (Dantoft et al., 2017; Fulkerson et al., 2021; Lynn et al., 2023; Nogalski et al., 2014). In this study, we looked into the relationship between the IL-33 levels & CMV infection in recurrent pregnancy loss in women from Iraq.

2. Materials and Methods

2.1. Patients & Sample Collection

60 case with RPL served as the case group in this case-control research, while 60 healthy controls gave birth without incident. Women aged 20 to 42 who had at least two consecutive abortions prior to Twenty weeks of pregnancy and were diagnosed with RPL made up the case group. Additionally, as healthy controls, women who had at least two successful pregnancies and were free of autoimmune disorders, endocrinopathies, steroid therapy, or inflammation were chosen. Interviews and questionnaires were used to gather data from the case and control groups on clinical traits and lifestyle.,. The women who were chosen for this study were all from Karbala city. As required by ethical standards, all study participants were informed about the study and the consent form.

Leave the blood undisturbed at room temperature to allow it to clot after the whole blood has been collected. Usually, this takes twenty minutes. then Centrifuging (Thermolas Scientific, C-12000) at 2,000–3,000 rpm for twenty minutes to remove the clot. Use the BioTek 50 TS ELISA washer and the BioTek 800 TS ELISA reader.

and Sun Long Biotech Co., LTD's Human Interleukin 33 (IL-33) ELISA Kit , Standard diluents (150µl) are added to dilute the standard (270 pg/ml) to 180 pg/ml, 120 pg/ml, 60 pg/ml, 30 pg/ml, and 15 pg/ml. Sandwich-ELISA mode is the technique used with this ELISA kit Using spectrophotometry, the optical density (OD) is determined at a wavelength of 450 nm and Camp medica CMV IgG \ Romania , Camp medica CMV IgM \ Romania Using spectrophotometry, the optical density (OD) is determined at a wavelength of 450 nm.

2.2. Statistical Analysis

The statistical package for the social sciences (SPSS) software (version 21.0) was used to do the statistical analysis of the collected data. The relationship between the examined IL-33 and RPL risk was examined using logistic regression. $p < 0.001$ was established as the threshold for statistical significance.

3. Results

3.1. Distribution of Age and BMI in Patients and Control

mean age of case as mentioned in Table 1 was less than the mean age of control (29.267 years vs 29.683 years, P. value = 0.74842) There are non-significant statistical differences between patients & control group, Table1. mean BMI of control more than mean age of case (24.218 vs 23.588) non-significant difference in BMI between the two groups (P. value =0.43023). Table1, Fig.1

Table1: Distribution and Characteristics of Patients and Control According to the Study Subjects

Parameters	Groups	Mean	Std. Deviation	P. value
Age	Control	29.683	7.203	0.74842
	Patients	29.267	6.994	
BMI	Control	24.218	4.990	0.43023
	Patients	23.588	3.617	
Independent T-Test and Mann-Whitney U test have been utilized to conduct a comparative analysis between two groups on the same continuous variable.*. The mean difference is significant at the 0.05 level." **. The mean difference is significant at the 0.01 level."				

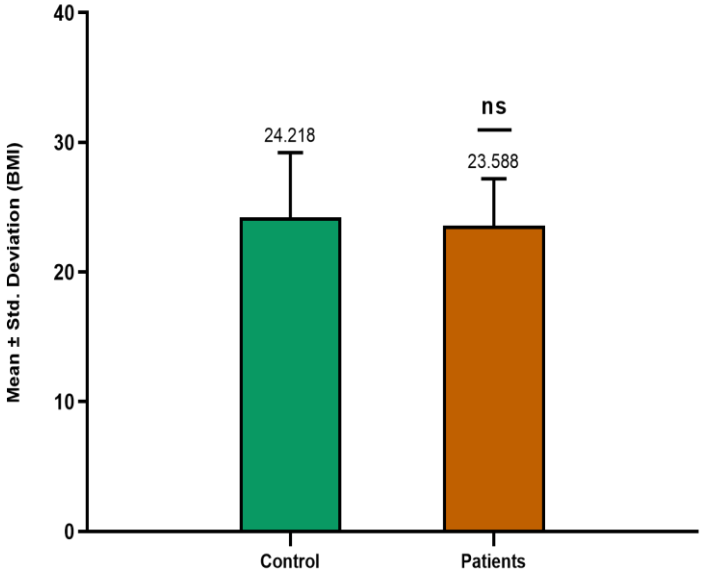

Figure1: Comparison of BMI Between Male and Female Patients

3.2. Measurement of CMV IgM & CMV IgG in Patients and Control by ELISA

IgM CMV mean in patient more than control (0.378 vs 0.212) significant p= 0.01848*. IgG CMV mean in patient more than control (1.232 vs 0. 717) significant p= 0.00001**. by this results the CMV IgM & IgG important risk factor in RPL. Table2, Fig.2.

Table2: The Comparison Between Research Parameters in Patients and their Controls

Parameters	Groups	Mean	Std. Deviation	P. value
CMV IgM	Control	0.212	0.135	0.01848*
	Patients	0.378	0.115	
CMV IgG	Control	0.717	0.108	0.00001**
	Patients	1.232	0.169	
Independent T-Test and Mann-Whitney U test have been utilized to conduct a comparative analysis between two groups on the same continuous variable. *. The mean difference is significant at the 0.05 level, **. The mean difference is significant at the 0.01 level				

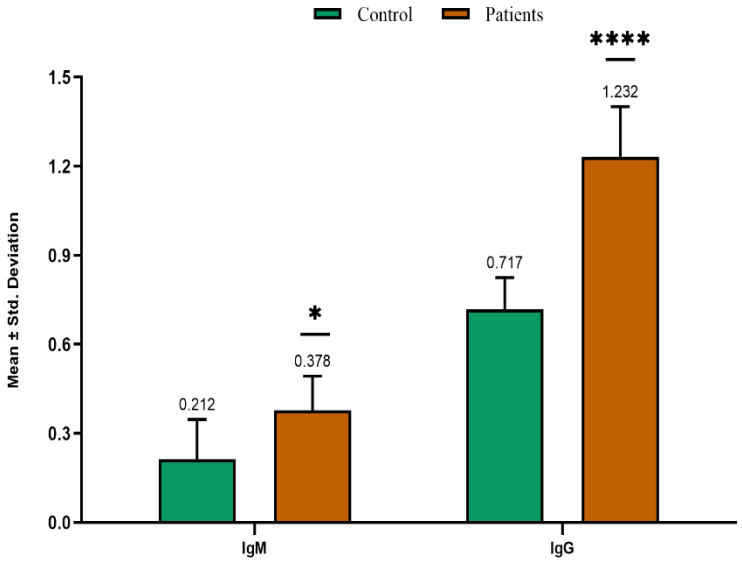

Figure2: Mean Cytomegalovirus (CMV) IgM and IgG Antibody Levels in Patients Versus Controls

The bar chart compares the mean ± SD titres of CMV-specific antibodies between patient and control groups. Patients show a modest but significant elevation in IgM (0.378 ± SD) relative to controls (0.212 ± SD; $p < 0.05$). A pronounced increase is observed for IgG, with patients (1.232 ± SD) far exceeding controls (0.717 ± SD; **** $p < 0.0001$). Error bars represent standard deviation; asterisks denote statistical significance (**** = $p < 0.0001$, *

3.3. Measurement of IL-33 in Patients and Control by ELISA

IL-33 mean in patient less than control (6.782vs 8.781) significant p= 0.00129**. by this results the IL-33 important protective factor in RPL Table3, Fig.3.

Table3: The Comparison Between Research Marker (IL-33) in Patients and Their Controls

Parameters	Groups	Mean	Std. Deviation	P. value
IL-33	Control	8.781	4.363	0.00129**
	Patients	6.782	1.534	
Independent T-Test and Mann-Whitney U test have been utilized to conduct a comparative analysis between two groups on the same continuous variable. *The mean difference is significant at the 0.05 level. **The mean difference is significant at the 0.01 level				

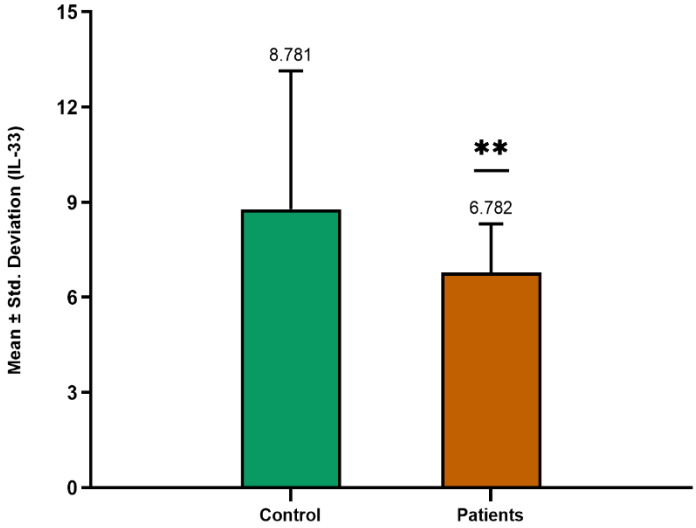

Figure3: Comparison of Serum IL-33 Levels Between Patients and Controls
The bar chart illustrates the mean concentration of interleukin-33 (IL-33) in patient and control groups. Patients exhibit significantly higher IL-33 levels (118.1 ± SD) compared to controls (88.4 ± SD), with the difference reaching statistical significance (p<0.01). Error bars represent standard deviation; asterisks indicate statistical significance.

4. Discussion

According to some research, pregnant women who have experienced a miscarriage show significantly lower levels of interleukin 33, making it an important indicator of the success of the pregnancy because human endometrial stromal cells (HESCs) must activate the IL-33/ST2 pathway in order for a pregnancy to be successful but another study found the IL-33 increase in abortion more than in healthy deliver (Salker et al., 2012).

The same applies to cytomegalovirus infection. Previous research has shown that this viral infection causes problems for both the fetus and the pregnant woman, including recurrent miscarriages (Kareem et al., 2022),

Both in vivo and in a multicellular ex vivo model, CMV infection alters the placental immunological milieu, indicating that CMV-induced cytokine modulation may be a cause or aggravating factor of placental and fatal harm (D'Antonio et al., 2023; Kareem et al., 2022; Njue et al., 2021). CMV was capable of invading several placental cells in vitro. Destroying the trophoblastic progenitor stem cell (syncytium and cytotrophoblast precursor), which decreases the number of mature cells, the extra villous trophoblast cells (floating cytotrophoblast), which invades the uterine vascular wall and is in charge of remodelling the circulation during pregnancy, would have a negative impact on the pregnancy because it would decrease maternal blood circulation in the placenta, which would lessen fatal growth restriction or even miscarriage. Additionally, CMV possesses immunomodulatory qualities that change the host immunological response and disrupts important autoregulatory mechanisms in the cytotrophoblast, which would change trophoblast migration. Preterm labour, fatal development

limitation, and miscarriage could result from these changes. Development restriction in embryos unaffected by CMV whose mothers have been diagnosed with the disease can also be explained by the fact that CMV raises tumour necrosis factor- alpha levels in vitro, which causes increased trophoblast death (D'Antonio et al., 2023; Hamilton et al., 2012; Le-Trilling et al., 2023; Zischke et al., 2017), As gestational age increases, the risk of fatal infection rises, most likely as a result of cytotrophoblast differentiation. With a preference for the reticuloendothelial cells & central nervous system (CNS), the virus finally replicates in the tubular epithelium of the fatal kidney after passing through the placenta, the first organ to become infected. Placental infection, maternal viremia, and fatal dispersion through the hematogenous route are the likely sequence of events (lasting 7 to 8 weeks) that result in fatal infection (Fisher et al., 2022; Shahar-Nissan et al., 2020; Zischke et al., 2017). mean BMI of control more than mean age of case this result agrees with study that found non-significant between BMI and RPL and disagree with study that found increase BMI in patient more than control. The inconsistent results across studies may be due to differences in study design and demographic factors; sample sizes may vary significantly between cross-sectional and longitudinal research, which affects statistical power and generalizability; some studies consider three or more losses, while others consider two or more; and population variations also play a role; factors such as genetic background, access to healthcare, and diet can have a significant impact on results and may explain why BMI is considered a risk factor in some contexts but not in others(Eapen et al., 2021) .mean age of case as mentioned in Table 1 was less than the mean age of control There are non-significant statistical differences between patients and control group , this result agree with another study the age non-significant with recurrent abortion. but disagree with study found the age play role in abortion. Variations in study design and demographic variables may be the cause of the inconsistent results among studies. Sample sizes might differ significantly between cross-sectional and longitudinal research, which impacts generalizability and statistical power. Furthermore, whereas some research calls for three or more losses, others take into account two or more. Population variations also come into play; variables like genetic background, access to healthcare, and diet can have a big impact on results and could be the reason why age is seen as a risk factor in some contexts but not in others (Eapen et al., 2021; Yue et al., 2016).

5. Conclusions

In general, our research showed that among women in Karbala City, IL-33 level and cytomegalovirus infectious was linked to RPL risk. But the BMI and Age non-significant to link with RPL. Therefore, more research on various regions with higher sample sizes is advised to identify the impacts of BMI, RPL, IL-33, cytomegalovirus on RPL in order to better understand the link with RPL.

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