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Algorithm for Prevention of Recurrent Pregnancy Loss and Adverse Pregnancy Outcomes in Patient with Inherited Thrombophilia

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Abstract:
Pregnancy-related complications such as recurrent pregnancy loss, recurrent implantation failure, preeclampsia, intrauterine fetal growth restriction, and gestational diabetes pose significant risks to both maternal and fetal health. Emerging evidence suggests that genetic variations may contribute to the etiology of many of these conditions.
Understanding the interplay between genetic mutations and pregnancy complications can enhance risk assessment and enable personalized medical management for affected individuals. Further research is needed to better elucidate these relationships and guide clinical decision-making.
The objective of this study is to emphasize the medical implications of detecting congenital abnormalities in pregnant women and to underscore the importance of risk prediction, early diagnosis, and personalized care in improving maternal and fetal health outcomes. This comprehensive analysis underlines the critical role of algorithms in preventing severe pregnancy-related complications and enhancing targeted interventions in obstetric care. By elucidating the intricate pathogenesis of these conditions, the study provides valuable insights for improving specific therapeutic approaches.

Keywords: Preeclampsia (PE), Gestational Diabetes (GD), Intrauterine Growth Restriction (IUGR), Genetic Mutations Factor V Leiden (FVL), Angiotensin-Converting Enzyme (ACE,) PAI-I 4G/4G

1. Introduction

There is an increasing interest in understanding how maternal genetics may play a role in the development of pregnancy-associated complications. The most significant concerns for both maternal and fetal health are preeclampsia, intrauterine growth restriction (IUGR), and gestational diabetes. These conditions arise from complex interactions involving genetic factors in the mother and fetus, environmental influences, and lifestyle choices [1]. The importance of maternal genotype in the etiology and pathophysiology of various diseases is becoming clearer as researchers dive further into the molecular processes driving these diseases.

Preeclampsia (PE) is a hypertensive disorder specific to pregnancy that typically occurs after 20 weeks of gestation. It is characterized by elevated blood pressure and the presence of proteinuria. Preeclampsia can present with a range of symptoms and may lead to complications for both the mother and fetus if not managed properly [2]. It is a foremost source of maternal and newborn morbidity and death, affecting around 5-9% of pregnancies globally. The exact cause of PE is still unknown despite substantial studies being done to pinpoint the underlying processes. However, a growing body of research suggests that genetic variants in mothers may increase susceptibility to preeclampsia [3]. Understanding the probable genetic susceptibility that underpins the pathophysiology of PE has been made possible by research into candidate genes and genetic polymorphisms.

Intrauterine growth restriction (IUGR) is another significant condition that can impact fetal development. It is characterized by a birth weight below the 10^{th} percentile for the gestational age of the fetus [4]. IUGR poses a risk to the newborn's long-term health, as it can lead to developmental delays and an increased risk of chronic illnesses later in life.

The condition arises when the fetus does not receive adequate nutrients and oxygen from the placenta, which may result from maternal, fetal, or placental factors. These can include maternal health conditions such as hypertension, diabetes, or malnutrition, as well as issues with placental function or fetal health problems. An important contributing element to the development of IUGR seems to be the interaction between maternal genetics and placental function. Knowing the genetic factors affecting placental growth and function may open new doors for early identification and treatment, eventually enhancing fetal outcomes [5].

Gestational diabetes mellitus (GDM), is a kind of diabetes that manifests itself in pregnant women who have not previously been diagnosed with diabetes. Diabetes mellitus is characterized by decreased insulin production and increased insulin resistance, which ultimately result in raised blood glucose levels [6]. GDM poses risks to the maternal and fetal health and increases the likelihood that both the mother and the growing fetus could experience metabolic problems during pregnancy and in the future. Unraveling the genetic basis of GDM has been a main focus of study due to the possibility that identifying susceptible genes would allow for the creation of individualized preventative methods and targeted therapeutics [7]. By undertaking a comprehensive evaluation of pertinent studies, the developers will highlight the current level of knowledge, identify key genetic factors involved in these illnesses, and assess the potential implications for clinical practice and public health [8].

According to pathological and clinical research, the placenta seems to be a crucial actor in the pathogenesis of PE; nevertheless, the precise origin of this condition is still a matter of discussion at this time. The development of PE may be identified by abnormalities in placentation and angiogenesis [9]. A definitive statement has not been made on the dynamic changes that occur in protected cells at the maternal-fetal edge. Few studies have evaluated changes in immune cell proportions that occur in the middle and later stages of pregnancy, despite the fact that several studies have revealed shifts in the scope of protected cells present in the regular maternal-fetal boundary during the early period of pregnancy [10].

2. Methods

2.1.Maternal genotype

The genetic makeup of an individual organism, specifically the genes inherited from the mother, is referred to as the maternal genotype. This represents the unique genetic information contained within an individual's DNA that originates from the maternal side. Genes are segments of DNA that encode instructions for constructing and maintaining the body. They play a key role in regulating a variety of traits and characteristics in an organism.

The maternal genotype contributes to an individual's overall genotype, which is composed of a specific combination of genes inherited from both parents. The maternal genotype influences how various morphological, physiological, and behavioral traits are expressed and developed. This can include aspects such as susceptibility to certain diseases, growth patterns, and even behavioral tendencies. Understanding the maternal genotype is important in studying hereditary patterns, as well as in assessing the risk of genetic disorders and conditions that may affect the offspring. Advances in genetic research and technology have enabled scientists to better analyze the maternal genotype and its impact on an individual's development and health [11].

Genes are organized into pairs and located at specific positions (loci) on chromosomes. Each gene pair consists of one gene inherited from the individual's biological father and one gene inherited from the biological mother. Although genes may exist in pairs, not all genes express themselves equally; some may be recessive or silent in the presence of a dominant counterpart. Consequently, the maternal genotype may not always be immediately obvious in an individual's appearance.

Nevertheless, an individual's phenotype—observable traits and characteristics—is largely influenced by their maternal genotype. This impact is observed through the expression of certain genetic traits and predispositions to certain health conditions.

The study measured various indicators of hereditary thrombophilia, including PAI-1 4G/4G, ACE D/D, and ACE I/D polymorphisms, as well as homocysteine levels, in blood samples from all participants. Variations in the Factor V Leiden, MTHFR, and prothrombin genes have been associated with inherited predispositions to thrombophilia and other related conditions.

Understanding these genetic factors and their impact on an individual's health can provide valuable insights for the prevention, diagnosis, and treatment of associated conditions. Further research into these genetic variations and their interactions with other factors may lead to improved medical management and outcomes for affected individuals. The following characteristics were used to exclude women from the study: history of multiple pregnancies; history of a major anomaly in a previous fetus; greater risk of obstetric problems (hyperprolactinemia, thyroid dysfunction, chronic hypertension, SLE, or other systemic illnesses), body mass index (BMI) 30 or higher in females.

2.2.Genetic mutation

The terms we mentioned are connected to genetic variants and mutations linked to some medical disorders, particularly those related to blood clotting and cardiovascular conditions in pregnant women. Let's dissect them:

- ACE D/D: Angiotensin-Converting Enzyme is referred to as ACE. A particular genetic variation of the ACE gene is called the D/D genotype [12]. It has been researched about hypertension (high blood pressure) and cardiovascular illnesses.
- ACE I/D: A different form of the ACE gene, denoted here by the letters "I" for insertion and "D" for deletion [13]. It's also linked to heart disease and high blood pressure.
- PAI-1 4G/4G: PAI-1 stands for Plasminogen Activator Inhibitor-1, which regulates blood clotting [14]. The 4G/4G genotype of PAI-1 is associated with increased levels of PAI-1, which may lead to an increased risk of thrombosis (formation of blood clots).
- Prothrombin gene mutation: Blood clotting depends on a protein called prothrombin. Increased prothrombin and an increased risk of thrombosis can result from mutations in the prothrombin gene, most notably the prothrombin G20210A variant [15].
- MTHFR: MTHFR refers to the enzyme methylenetetrahydrofolate reductase, which plays a role in the breakdown of the B vitamin folate. There may be problems with folate metabolism if you have a mutation in the MTHFR gene that lowers enzyme function [16]. The evidence linking these mutations to an increased risk of blood clots and cardiovascular illness is inconclusive, but it has been reported in several studies.
- FVL: The mutation in the Factor V gene is known as Factor V Leiden (FVL). Blood clotting relies on a protein called factor V [17]. Abnormal blood clots are more likely to form in people with the FVL mutation.

Although certain people may be more susceptible to particular diseases because of their genes, other factors, including lifestyle, environment, and even more genes, can determine an individual's general health.

2.3.Risk factors

Maternal genetics and environmental factors interact to increase or decrease the likelihood of complications such as preeclampsia, IUGR, and gestational diabetes. Examining the possibility of a link between maternal genotype and the following conditions:

2.3.1. Preeclampsia

High blood pressure and organ damage, most often to the kidneys and liver, characterize preeclampsia, a dangerous pregnancy complication [18]. The 20th week of pregnancy is a common time for this to happen. Genetic predisposition is thought to have a role in

predisposing certain women to preeclampsia. However, the specific etiology of the syndrome is yet unknown. PE risk factors can be inherited from the mother, including genetic variations [19]. Genetics has a role in preeclampsia, but it's crucial to remember that other factors, like maternal health, preexisting diseases, and environmental effects, all play a role.

PE is a placental condition that impacts both the mother and the developing child. It causes problems in 6-8% of pregnancies [20]. At 20 weeks of pregnancy, a 24-hour protein urine test of 300 mg/day, or 1+ proteinuria, discovered by visual dipstick, and new-onset hypertension (systolic blood pressure 140 mm Hg and diastolic blood pressure 90 mm Hg recorded on two separate occasions every four hours) are diagnostic of PE. In addition to proteinuria, other symptoms of new-onset hypertension include renal failure, HELLP syndrome, pulmonary edema, and neurological issues include vision loss and cognitive deterioration [21]. This disease is still a leading reason for maternal mortality and morbidity around the world. This is true in both industrialized and developing nations. According to the World Health Organization, between 1.8% and 16.7% of maternal deaths occur because of this multisystem illness in underdeveloped countries, including Bulgaria, the United Kingdom, and Germany [22]. Reduced uteroplacental perfusion due to aberrant cytotrophoblast invasion of spiral arterioles is thought to be the underlying cause of hypertension, acute hemolysis, increased liver enzymes, and low platelets (HELLP syndrome) [23]. PE is more common in women with a family history of the disorder and women whose mothers also suffered.

Pathophysiology of Preeclampsia

The placenta plays a crucial role in the development of preeclampsia. It has classified PE as a 2-stage model disease, with the first stage characterized by a disruption in placentation caused by a failure of cytotrophoblast cells to invade the spiral arteries [24]. Placental ischemia and reperfusion (stage 2) increase oxidative stress due to increased reactive oxygen species, cytokines, and oxygenation [25]. This sets off the body's innate immune system, leading to the organ-specific alterations seen in preeclampsia. PE causes proteinuria, edema, clotting, eclampsia, HELLP syndrome, and hypertension by activating many pathophysiological pathways that affect multiple organ systems, including the renal, hepatic, hematological, central neurological, and cardiovascular systems. While the exact cause of PE is unknown, aberrant placentation has been implicated as a key player in the disease's pathogenesis [26].

2.3.2. Intrauterine Growth Restriction (IUGR)

A fetus IUGR does not develop normally during pregnancy. The infant may have a lower birth weight and be at greater risk for developing several health problems. Some research suggests genetics play a role in determining IUGR risk [27]. An increased risk of IUGR may result from maternal genetic variants associated with variables influencing fetal growth and development. Furthermore, maternal health and the environment's state both significantly affect fetal growth and are potential contributors to IUGR.

2.3.3. Gestational Diabetes

Hyperglycemia and hyperinsulinemia result from carbohydrate intolerance, which manifests during pregnancy and is known as gestational diabetes mellitus (GDM) [28]. The second trimester of pregnancy is a common time for it to display. Although GDM resolves itself after giving birth, it puts both the mother and the child at risk for developing type 2 diabetes later in life. There is a correlation between increased risk and the undetected existence of either type 1 or type 2 diabetes [29]. Insulin resistance manifests in various ways in people with type 2 diabetes (T2D), including genetics, lifestyle choices, and excess body fat. In 1980, the prevalence of T2D was 4.7%, but by 2014, it had climbed to 8.5%. The failure of pancreatic-cells to produce and secrete insulin due to autoimmune damage characterizes type 1 diabetes. Because of this, people with type 1 diabetes must inject insulin regularly to maintain their health. Obesity, a BMI of 30, a previous diagnosis of gestational diabetes, a history of complications during pregnancy, macrosomic deliveries, persistent glycosuria and proteinuria, and a history of spontaneous abortions are all risk factors for gestational diabetes [30].

2.3.3.1.Pathophysiology of GDM

The pathogenesis of GDM includes meta-inflammation and insulin resistance (IR).

Increases in IR of 40–50% are common during a healthy pregnancy, while increased insulin secretion of 200–250% ensures that glucose levels remain within normal range. Cell dysfunction is assumed to play a factor in the development of gestational diabetes, albeit this is yet only speculation. Uncontrolled surges in insulin production by the pancreatic cells during pregnancy have been linked to gestational diabetes [31]. Maturity-onset diabetes in the young (MODY) is caused by a dysfunctional -cell that can be inherited in an autosomal dominant form. These variations likely manifest themselves subtly, are found in preexisting diabetes, and are identified by prenatal glucose screening [32]. The body's inflammatory response may also influence GDM. It undergoes a metamorphosis in normal pregnancies and, if the reaction is highly pronounced, can lead to complications for the mother. These include premature labor, high blood pressure in the mother, eclampsia, and gestational diabetes. Obesity may increase the body's inflammatory response. When compared to normal-weight women, cytokines are released at a higher rate from obese women into the bloodstream [33]. Recent research has shown that pregnant obese women had higher levels of inflammatory markers such interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor (TNF), and C-reactive protein (CRP). Among other things, oxidative stress has been linked to inflammation.

2.3.3.2. Oxidative Stress and Pregnancy-Related Diabetes

When prooxidants outnumber antioxidants in a cell, oxidative stress occurs. Free radicals and nonradical oxygen derivatives are expressed via prooxidants, also known as reactive oxygen species (ROS) [34]. Hydroxyl radical (OH), organic hydroperoxide (ROOH), Hydrogen peroxide (H2O2), superoxide anion (O2), then many more are all reactive oxygen species. It has been found that women with GDM produce more free radicals in their bodies than women without the condition. 8-isoprostane is released at a higher rate from the placentae of women with GDM than women carrying healthy pregnancies.

Furthermore, 8-isoprostane was positively correlated with plasma glucose, suggesting a link between lipid peroxidation and glycaemic control. The placentae of women with GDM surprisingly showed decreased sensitivity to oxidative stress. After oxidative stress was applied to the placentae of women with GDM and normotensive blood pressure, the normotensive women's placentae released twice as much 8-isoprostane as the GDM women's placentae [35]. It was hypothesized that this was because of the modest oxidative stress experienced by the developing baby, which led to the accumulation of antioxidants in the placenta [36]. Uric acid, glutathione, Vitamin C, and lipoic acid are all examples of water-soluble antioxidants. Lipid-soluble antioxidants, which can be taken from the diet or synthesized by the cell, are also present. Antioxidants such as carotenes, ubiquinol (coenzyme Q), and vitamin E offer cellular protection against lipid peroxidation. Individuals with poor glycemic control have higher lipid peroxidation levels. Figure 1 depicts the flowchart of the relationship between oxidative stress and hyperglycemia.

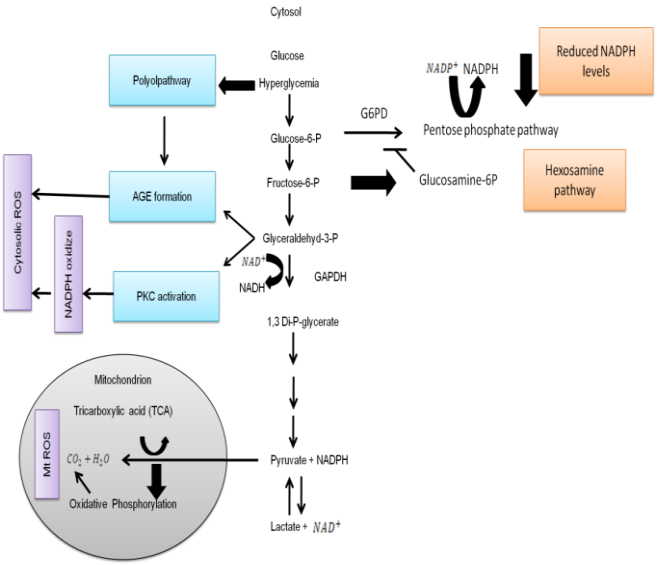

Figure 1: Flowchart illustrating the relationship between oxidative stress and hyperglycemia

Genetic susceptibility, maternal health and lifestyle, and environmental variables all have a role in developing complications such as PE, intrauterine growth restriction, and gestational diabetes. Regular prenatal care visits and close collaboration with healthcare experts can help pregnant women mitigate risks and have a safe pregnancy.

3. Risk factors leading to Adverse Pregnancy Outcome, (PE, IUGR, GDM)

1. Mother's age >35 years.

2. Smoking > 10 cigarettes/day
3. BMI > 30 kg/m2
4. Family history (first relative up to 50 years of age)
4.1. Varicose veins of the lower limbs
4.2. Hypertensive disease
4.3. Myocardial infarction, Ischemic stroke, BTE, Deep venous thrombophlebitis
5. Personal history of the patient
5.1. Varicose disease
5.2. Myocardial infarction, Ischemic stroke
5.3. Pulmonary thromboembolisam
5.4. Deep venous thrombophlebitis
6. Obstetric history
6.1. Early fetal loss <10 g.w., 2 or more
6.2. Late fetal losses up to 24 g.w.
6.3. History of stillbirths
6.4. Preeclampsia moderate/severe
6.5. Abruption of the placenta
6.6. Fetoplacental insufficiency (Fetal growth restriction)
7. Somatic status
7.1. Dysmetabolic syndrome
7.2. Inflammatory diseases of the urinary tract
7.3. Chronic hypertensive disease
7.4. Diabetes mellitus with vascular damage
7.5. Diseases of the thyroid gland
8. Thrombophilia (gene mutations)
8.1. Factor V Leiden gene mutation
8.2. Mutation in the prothrombin gene G20210A
8.3. Antithrombin III, Protein C and Protein S deficiency
9. Thrombogenic polymorphisms
9.1. Genetic variant C677T in the Methylenetetrahydrofolate reductase gene
9.2. Genetic variant in the gene of Plasminogen activator inhibitor 1 (PAI-1) (carriage of genotype 4G/4G)
9.3. Angiotensin-converting enzyme - ACE D/D.
10. Function of the trophoblast
10.1. Low levels of PAPP - A
10.2. Low levels of PLGF
11. Immunological disorders
11.1. NK cells phenotype
11.2. LA
11.3 Antiphospholipid syndrome
12. Hypovitaminosis
12.1. Low level Vit. D
12.2. Low level Vit. B12

4. Algorithm for prevention of adverse pregnancy outcome

4.1. Table 1: First stage. Pre-Gestational management

6 months before planning of pregnancy

Investigations	**Preventive and curative measures**
1.Gynecological examination 2. FBC + Coagulation 3. Microbiology of vaginal content, cervix and uterus (Microbiota). 4. Hormonal status (LH, FSH, Estradiol, Prolactin, 4-androsendion, Testosterone, Progesterone) 5. TSH, anti TG, anti TPO 6. AFA, ANA, 7. NK Cells phenotyping 9. Vitamins (D and B12) 10.Thrombophilia spectrum 11. Consultation with genetics and Hematologist if necessary	1. Treatment of accompanying diseases and disorders in the coagulation status 2. Treatment of genital microbiome 3. Hormonal treatment in case of disorders 4. TSH <2.5 microE/ml, negative ant TG and anti TPO. 5. Normal immunological status 6. Weight control ..... - Antioxidants - Omega 3 fatty acids - Low Dose Aspirin 75-100 mg (15-25 day in second phase of the menstrual period) - Intralipid Sol. i.v. infusion before ovulation/ embryo transfer, if NK peripheral cells are high or Immunoglobulins (IVIG). - Folic acid not les then 4 mg/Daly (in cases with MTHFR C677T not less than 8 mg/Daly) - in cases with high D-dimers – Nattokinase

4.2. Table 2: Gestational management during pregnancy

Investigations	Preventive and curative measures
1. First stage + 2. First trimester screening for aneuploidies, Pre-eclampsia, gestational diabetes and preterm birth 11-13^{+6} g.w. 3. Oral glucose tolerance test in 12 g.w. in obesity patients with anamnesis of diabetes mellitus in first line relatives and in 24-28 g.w. 4. Control of Hemostasis on every 3-4 weeks 5. Doppler of Uterine artery: 11-13 g.w., 20-22 g.w., 30-33 g.w. 6. Ultrasound of feto-placental unit Ultrasound of cervical lent at 16 and 20-22 g.w.	First stage + - Polyvitamines - Tocolytics + spasmolitics - Progesterone not more than 300 mg per day in case of high risk Thrombophilia if need - Treatment of anemia - Correction of hemostasis **LMWH 0.3/0.4 depend of the D-dimer and aPTT, anti Xa** **Aspirin 100/150 mg or Nattocinase** - Corticosteroid prophylaxis in case of preterm birth - CTG monitoring 2 times weekly after 32 g.w. - Hospitalization on 37-38 g.w. - In heterozygous patient we stop LMH one week before term for delivery, if d-dimer and aPTT is in normal rates. - Stop LMH 12 hours before cesarean delivery in high risk Thrombophilia patients - Stop Aspirin and Nattocinase in 35 g.w.

4.3. Table 3: Prevention of complications in the puerperal period

Investigations	Preventive and curative measures
FBC + coagulation	- Early movement of the patient - Start with the LMH on the 6 hour after delivery - In patients with monogenic or heterozygous Thrombophilic gene mutations and normal D-dimers, fibrinogen, aPTT and anti X a, we start with Nattocinase 4 weeks pos partum - In Homozygous patients with family history for DVT, Pulmonary thrombosis, Myocardial infarction, Stroke, Personal history for thrombosis,obesity, We start with LMH at the 6 th hour. 6 weeks postpartum.

5. Conclusion

These results support the hypothesis that RPL, RIF, PE, IUGR and GDM are important in the global burden of maternal and fetal illness and mortality. Polymorphisms, or gene changes, set the stage for the emergence of multifactorial pathology. The human hemostasis system is highly sophisticated and adaptive. Such polymorphisms can play a most important role in the pathology of pregnancy and delayed embryonic development when they combine with faulty functionally compromised alleles against the action of adverse (provoking) environmental stimuli. Gene mutations have been linked to impaired beta-cell function and sub-cellular insulin signaling, which may contribute to type 2 diabetes. The aspects based on genotyping have been adopted for the future of PE, IUGR and

GDM. It is also important to sequence the genes for TNF-alpha and antithrombin-1 activation to look for mutations that could cause overexpression of these factors and contribute to the unchecked creation of reactive oxygen species (ROS) in pregnant women with hereditary thrombophilia.

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