



The Role of Gestational Management and use of LMWH and Aspirin in Patients with Inherited thrombophilia

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Abstract: Recurrent pregnancy loss (RPL) is multiple pregnancy losses. Inherited thrombophilia, which increases blood clot risk, contributes to RPL. Pre-gestational therapy with Low-Molecular-Weight Heparin (LMH) and Aspirin may improve pregnancy outcomes in these patients. This study aims to evaluate the effectiveness of pre-gestational management and the combination of LMH and Aspirin in patients with RPL and inherited thrombophilia. A hereditary thrombophilia test was performed on each of the 459 pregnant research participants, whose gestational ages ranged from 6 to 38 gestational week Medical center - Prime Clinic and KIRM- Pleven in Bulgaria period from January 2021- May 2023 were collected. Based on the treatment method, patients in a dataset with RPL and hereditary thrombophilia were split into three groups. Group I (Control) patients did not get any pre-gestational care or anticoagulant treatment. Group II: Patients who only received aspirin treatment with 100 mg. Group III: Patients receiving LMH and aspirin therapy. Compared to the treated groups (Group II and Group III), the pregnancy success rate was noticeably lower among the patients in Group I (Control). In addition, Group I experienced more thrombotic events than the groups that received treatment. Pre-gestational therapy with aspirin alone or in combination improves pregnancy outcomes and reduces thrombotic events in RPL and hereditary thrombophilia patients. LMH combined with aspirin may increase pregnancy success more than aspirin alone. These findings need further investigation and larger trials to maximize treatment for this patient population.

Keywords: pre-gestational management, recurrent pregnancy loss (RPL), Low-Molecular-Weight Heparin (LMH), inherited thrombophilia, Low-Molecular-Weight Heparin (LMH), Aspirin.

1. Introduction

Losing a pregnancy is a major tragedy that greatly impacts the couple that loses it. Recurrent pregnancy loss (RPL), characterized by its repeated occurrence and unknown etiology in 50% of instances, is a frustrating and difficult issue in reproductive medicine [1]. A miscarriage occurs when a pregnancy spontaneously ends in utero before the fetus is viable. This term covers pregnancies up to 23 weeks and six days; in contrast, several nations have a definition that covers pregnancies up to 20 weeks. Even though RPL was defined as the loss of three successive pregnancies in the “2011 Green-top Guideline from the Royal College of Obstetricians and Gynecologists”, 1, the organization's most recent draft guideline makes it clear that consecutive miscarriages are not required to qualify as recurrent miscarriage. Two or more clinical miscarriages are considered RPL by the “American Society for Reproductive Medicine (ASRM)” [2]. Negative outcomes are associated with all forms of diabetes:

“type 1 (T1 Diabetes mellitus), type 2 (T2 Diabetes mellitus)”, and pre-gestational (PGDM).

Pregnant women with pre-existing diabetes mellitus are more likely to experience surgical delivery, preterm labor, congenital abnormalities, stillbirth, perinatal mortality, macrosomia, prematurity, and cesarean section (CS). However, the caliber of treatment provided to women with diabetes mellitus can influence unfavorable birth outcomes by lowering congenital disabilities and stillbirths. Pregnant women with diabetes do better when they receive more support. The success of pregnancies is improved when women with pre-existing diabetes mellitus receive the proper therapeutic care [3]. Despite the increased risk of RPL among these women, routine screening for acquired or genetic thrombophilia is not always warranted if no venous thromboembolism has occurred. Due to a lack of knowledge regarding the factors that contribute to these pregnancy challenges and a lack of evidence demonstrating the effectiveness of therapies, it is challenging to assess if screening women who have had pregnancy issues is beneficial. The existence of this association with placental vascular thrombosis led

researchers to establish this notion. Conditions that become more likely as pregnancy progresses include preeclampsia, fetal growth limitation, early delivery, and stillbirth. Antiphospholipid syndrome (APS) is to blame for these complications since it leads to placental insufficiency and inadequate blood flow [4]. The term "thrombophilia" refers to a propensity to create clots unnecessarily. This syndrome makes it more likely that hereditary or acquired thromboembolic diseases, such as venous thromboembolism (VTE), may develop. Increased risk of venous or arterial thrombosis and complications in early or late pregnancy are hallmarks of "APS," a kind of acquired thrombophilia, all of which are connected to antiphospholipid antibodies (APAs).

Numerous studies have revealed the importance of APA and the impact of anticoagulant therapy in women with RF and APS. Recent research has shown that anticoagulant medication positively affects RPL women with APS in terms of live birth rate (LBR) and birth weight. Hereditary or inherited thrombophilia refers to diseases in which a genetic mutation impacts a coagulation system protein's quantity or function. Although it is clear that inherited thrombophilia contributes to vascular thrombosis, it is still debatable whether it affects women with RF [5]. Women frequently lack a clear understanding of miscarriage and why it keeps happening. The issue is underappreciated as a specific physical health concern, which typically has no negative health effects. However, the psychological effects of the incident are much more severe than the physical trauma and subsequent clinical presentation. Furthermore, many societies and traditional beliefs place a premium on a woman's ability to conceive and have children [6]. This research described the importance of pre-gestational treatment and the use of LMH and aspirin in patients with RPL and hereditary thrombophilia.

The study continues with the sections below: The literature review is offered in Section 2, followed by a description of the methodology in Section 3, an examination of the research results in Section 4, and finally, the conclusion in Section 6.

2. Literature review

The effect of vitamin D supplementation on the Treg/Th17 ratio in RPL patients was studied in the study above [7]. In a study [8], pregnant women with thrombophilia and a previous RPL completed online surveys to gauge intimacy problems, stress, and marital satisfaction. Recurrent preterm loss, or miscarriage before 24 weeks of pregnancy, is one of the most prevalent reproductive illnesses, affecting anywhere from 1 percent to 5 percent of women [9]. This study compared methylation levels in the MTHFR gene's promoter region with RPL and healthy, fertile women [10]. For their possible relevance in primary and secondary RPL and future losses to the same partner, chromosomal abnormalities were investigated [11]. Study [12] provided an understanding of the "etiopathogenesis of miscarriages" brought on by the hereditary type of thrombophilia. Chromosome variations, chromosomal polymorphisms, and genetic polymorphisms are just a few of the genetic traits linked to RPL presented in this study [13]. According to this research [14], the measurement of "antithrombin, protein S, and protein C activity, as well as other thrombophilia tests" is all affected by direct anticoagulants (DOACs). The study [15] determined the risk connected to these genes in the Indian population due to the widespread reporting of the function of many "thrombophilia-related genes and variants associated with RPL"-recurrent implantation failure (RIF).

3. Methodology

Recurrent pregnancy loss (RPL) is the term used to describe the loss of two or more pregnancies in a row before the 20th week of gestation. Additional considerations and treatment alternatives might be required in situations with RPL linked to hereditary thrombophilia. Genetic disorders called inherited thrombophilias raise the possibility of blood clot formation. Figure 1 depicts the flow of the methodology.

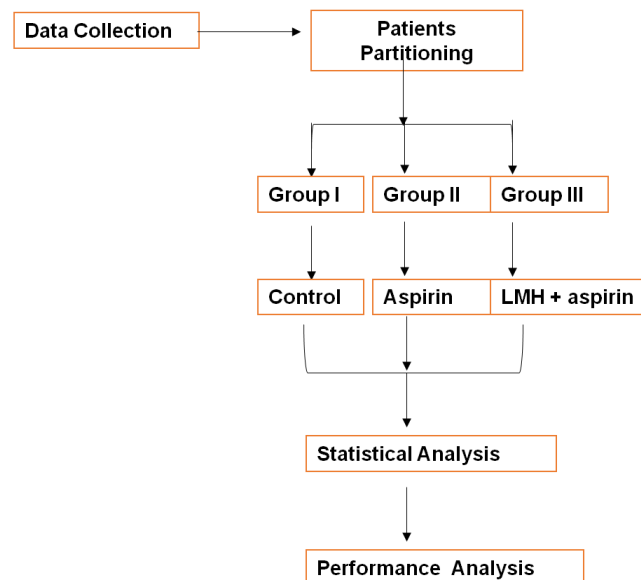


Figure 1: Flow of the methodology

3.1 Data collection

In Bulgaria, Burgas region, between January 2021 and December 2023, a prospective study was carried out at the Clinical Institute for Reproductive Medicine - Plenen and Medical Center-Prime Clinic - Burgas. With gestational ages ranging from 6 to 38 weeks, we included 459 pregnant women in the study (Investigated group n=309, Control group n=150).

3.2 Inclusion and exclusion criteria

- ❖ Factor V Leiden, MTHFR C677T, Prothrombin G20210A, PAI-I 4G/4G, and ACE D/D all have been linked to inherited variations in their respective genes.
- ❖ The following characteristics were used to exclude women from the study: history of multiple pregnancies; history of a major anomaly in a previous fetus; anomaly of the uterus, greater risk of obstetric problems (hyperprolactinemia, thyroid dysfunction, or other systemic illnesses), body mass index (BMI) 30 or higher in females.
- ❖ This study was approved by the Medical Center - Prime Clinic - Burgas and Medical Center Clinical institute for reproductive medicine, Snt. Elisaveta" Pleven in Bulgaria, and each participant gave their informed permission.

3.3 Data partitioning

The three groups in the data set are the control group, Group I, and Group III. The groups' subjects tested for hereditary thrombophilia were four hundred fifty-nine pregnant research volunteers. Patients receiving only 100 mg of aspirin treatment were assigned to Group II, while those receiving LMWH and aspirin treatment were assigned to study Group III.

3.3.1 Group I

Patients in Group I (the control group) did not receive any prenatal care or anticoagulant therapy before the start of their pregnancies. Pre-gestational care is medical attention and guidance given to women before they conceive to improve their health and spot any problems that could arise during pregnancy.

3.3.2 Treatment for Group II and III

- ❖ Aspirin and LMWH are two drugs that have various uses. In contrast to LMWH, a type of blood thinner intended to prevent blood clots; aspirin is frequently used for its effects on inflammation and platelets. These drugs directly impact neither body weight nor BMI. The general formula given before would be used to compute the body weight BMI with a 10% decrease:

$$BMI = \text{weight (in kilograms)} / (\text{height in meters})^2 \quad (1)$$

- ❖ Pregnant women with dysmetabolic syndrome should be treated carefully and under the direction of a healthcare provider using drugs such as aspirin and LMWH. The possible hazards and advantages of medicines must be carefully considered during pregnancy because it is a particular and delicate situation.
- ❖ Aspirin is usually reserved for high-risk diseases like preeclampsia in pregnancy. Low dosages of aspirin (typically 100 mg) may minimize pregnancy problems. A healthcare expert should evaluate the risks and benefits of the mother and fetus before prescribing aspirin during pregnancy.
- ❖ Pregnancy-related blood coagulation problems such as deep vein thrombosis are treated with LMWH. Pregnant women with dysmetabolic syndrome may be administered medication to prevent blood clots. A healthcare professional should carefully examine using LMWH during pregnancy based on the individual's circumstances.
- ❖ Pregnant women must receive thorough prenatal care and cooperate closely with their healthcare practitioner to manage the dysmetabolic syndrome. Diet, exercise, and weight management are key to managing dysmetabolic syndrome during pregnancy.
- ❖ A healthcare provider with experience treating thyroid diseases during pregnancy should be in charge of a pregnant woman's therapy for Hashimoto's thyroiditis if her TSH level is less than 2.5 milli-international units /L.
- ❖ Hyperhomocysteinemia in pregnancy can be treated with intravenous glutathione, vitamin C, and vitamin B complex infusions. Dietary changes and vitamin supplementation are usually used to treat hyperhomocysteinemia during pregnancy, depending on the reason and individual needs.
- ❖ In pregnant women, intravenous immunoglobulin G (IVIG) is the first-line treatment for antiphospholipid syndrome (APS). The anticoagulant and antiaggregant medication prevents blood clots and improves pregnancy outcomes for APS.
- ❖ Due to fetal development hazards, ACE inhibitors are not indicated for pregnant women with angiotensin-converting enzyme deletion/deletion (ACE D/D) genotype and hypertension. ACE inhibitors can harm embryonic growth and kidney development during the first, second and third trimesters.

- ❖ Pregnant women with hypertension or other medical conditions must work closely with their healthcare professional. Monitoring the blood pressure and evaluate fetal well-being to keep mom and baby safe.

3.3.3 Group II

Patients in Group II were those who received a daily aspirin dosage of 100 mg orally. A common drug with anti-inflammatory and antiplatelet effects is aspirin. It is frequently administered in low doses, such as 100 mg, for its antiplatelet properties. Low-dose aspirin is occasionally advised during pregnancy for some high-risk individuals to prevent issues like preeclampsia or fetal growth limitation. High blood pressure and organ damage are hallmarks of preeclampsia, a disease that often manifests after the 20th week of pregnancy. Fetal growth restriction is a situation where the fetus's growth ability is constrained. Low-dose aspirin use during pregnancy is normally decided individually, so patients must speak with their doctor before starting any pharmaceutical plan. Healthcare professionals weigh various variables when determining whether low-dose aspirin is safe and effective for a specific pregnancy, including the patient's medical history, risk factors, and general health.

3.3.4 Group III

Patients in Group III received 100 mg of oral aspirin as a subcutaneous injection and 40 mg of enoxaparin daily during pregnancy. Enoxaparin, as was mentioned earlier, is a type of LMWH. Blood clots, pulmonary emboli, and "deep vein thrombosis (DVT)" are all conditions that it is frequently used to treat. The daily subcutaneous injection dose of enoxaparin is 40 mg, which is the dosage. Patient-specific considerations and potential dangers, the healthcare professional chooses this dosage. Patients in Group III received 100 mg of oral aspirin in addition to enoxaparin. As previously discussed, low-dose aspirin is occasionally advised to prevent pregnancy-related problems such as preeclampsia and fetal growth restriction. The daily dose of aspirin used orally is 100 mg. Group III's enoxaparin and aspirin combination aims to offer a thorough strategy for preventing blood clot formation and lowering the risk of problems during pregnancy. Professionals in the medical field would have selected the appropriate treatment plan and dosages after carefully considering the patient's medical history, risk factors, and current health status.

Additionally, until the 16th week of pregnancy, except those with MTHFR C677T, all patients received 0,4 mg of folic acid daily. Carriers of MTHFR C677T polymorphism, received 4 mg methylated folic acid throughout pregnancy. There were prenatal screenings at the 11 - 13 ^{+ 6}th, weeks. Patients were assessed using ultrasonography throughout all tests and questions regarding potential pharmaceutical side effects. Enoxaparin was administered up to the delivery, while aspirin was administered until the 36th week of pregnancy. If the pregnancy ended before 24 gestational weeks, it was considered a miscarriage; if it ended after that point, it was considered a stillbirth. It was recorded how obstetric operations went and if there were any difficulties. GHT is hypertension occurring beyond 20 weeks of pregnancy without preeclampsia symptoms. Proteinuria (300 mg/day), low white blood cell count, high creatinine levels, abnormal liver enzymes, pulmonary edema, epigastric discomfort, eyesight or mental impairment, and seizures were all indicative of preeclampsia or any combination of these symptoms. A fetus was considered in IUGR if its birth weight fell below the fifth percentile for its fetal sex and

gestational week. Birth before the age of 37 was deemed a preterm delivery.

Polymerase chain reaction (PCR) was used to find the thrombophilia gene mutations. The DNA was taken out of the blood with a MagPurix blood DNA extraction kit 200. We determined the aPTT and lupus anticoagulant (LA) using an STA-Compact completely automatic coagulation device. A battery of PCR tests determined the polymorphic mutant genotypes (wild-type, heterozygous, and homozygous). Using enzyme-linked immunosorbent assays (ELISA) and competitive immunoassays (CIA) (QUANTA Flashassays, INOVA Diagnostic, Inc.), Several autoantibodies, including those against beta 2-glycoprotein (IgM and IgG), cardiolipin, and the nucleus, were detected. Chemiluminescence tests were used to determine the amounts of serum prolactin, TSH, and free T4 (FT4).

3.3.5 Statistical analysis

The statistical analysis for this study was performed using IBM SPSS Statistics Version 20, developed by Statistical Package for the Social Science. A one-way analysis of variance was conducted to examine the differences in demographics across Groups I, II, and III. The chi-square test was used to compare the obstetric outcomes of the three groups. The statistical results were

considered significant when the p-value was less than 0.05. Statistics can be represented by means and standard deviations.

3.3.6 ANOVA

Analysis of variance (ANOVA) is a statistical method used to extract meaningful subsets of data from large amounts of raw data, such as reports of variability. When there are three or more data sets, the correlation between the variables has been analyzed using one-way ANOVA. Traditional analysis of variance (ANOVA) F-statistic equals the mean squared error between the null model (based on the anthropocentric premise) and the full model. The least-squares method is used to determine which parameters have constant variances.

Result and discussion

The three groups had similar BMIs and ages. All three groups had more abortions on average than three, which was similar across the three groups. The demographic data and pregnancy outcomes for the groups are shown in Table 1. The three groups' mean miscarriage rates and live birth rates were comparable. Preeclampsia patients were more prevalent in Group III than in Groups I and II. Additionally, compared to Groups I and II, Group III had a considerably higher rate of patients with premature birth.

Table 1: Demographic information and pregnancy results for the groups

Factors	Group I	Group II	Group III	P-value
Age(years)	30.72±3.81	29.72±3.81	31.75±3.39	0.064
BMI(kg/m2)	26.35±3.21	25.02±2.98	26.44±3.81	0.164
Miscarriage	9	17	9	0.695
Stillbirth	1	3	1	0.857
Preeclampsia	6	53	38	0.043
Median gestational age of delivery(week)	38.6	37.3	37.9	0.117
Pretermbirth	3	16	4	0.047

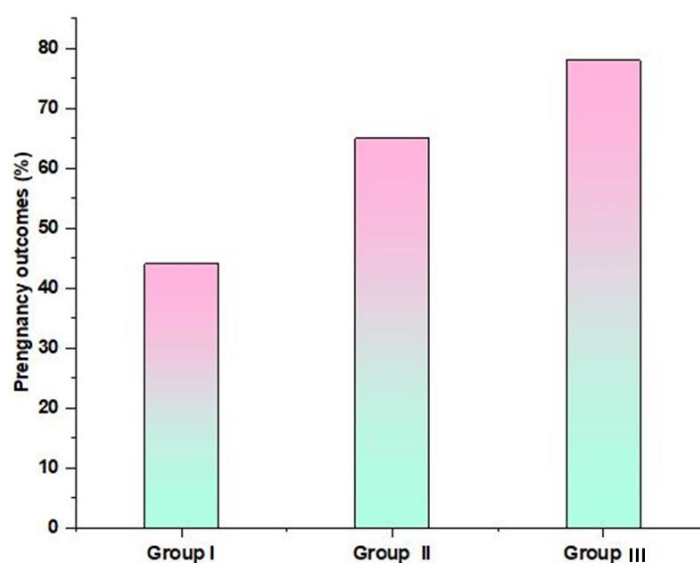


Figure 2: Pregnancy outcomes of various therapy groups

Figure 2 depicts the pregnancy outcomes of various therapy groups, such as Group I (control), Group II (aspirin alone), and Group III (LMWH with aspirin) can be compared to gain insight into the potential advantages and hazards of these therapies. Group I: Individual characteristics and medical issues may affect control group pregnancy outcomes. Without assistance, a woman's health and other risk factors may increase her chance of miscarriage, blood clots, and preeclampsia. Group II: For particular purposes, such as managing certain clotting problems or preventing preeclampsia, aspirin may be administered during pregnancy. In high-risk pregnant women, aspirin alone may reduce the incidence of preeclampsia. In rare circumstances, aspirin may lessen the risk of fetal growth limitation by increasing blood flow to the placenta. Group III: For recurrent miscarriage or preeclampsia prevention, LMWH is coupled with aspirin. Aspirin reduces inflammation and improves placenta blood flow, improving pregnancy outcomes. This combo medication may reduce preeclampsia, fetal growth limitation, and placental dysfunction problems. By lowering blood clots and enhancing placental function, LMWH plus aspirin may improve pregnancy success in people with recurrent miscarriages. Pregnancy outcomes depend on individual circumstances, medical issues, and other factors. Medical providers should advise pregnant women to use LMWH with aspirin or aspirin only. Group III suggested methods are more effective than groups I and II.

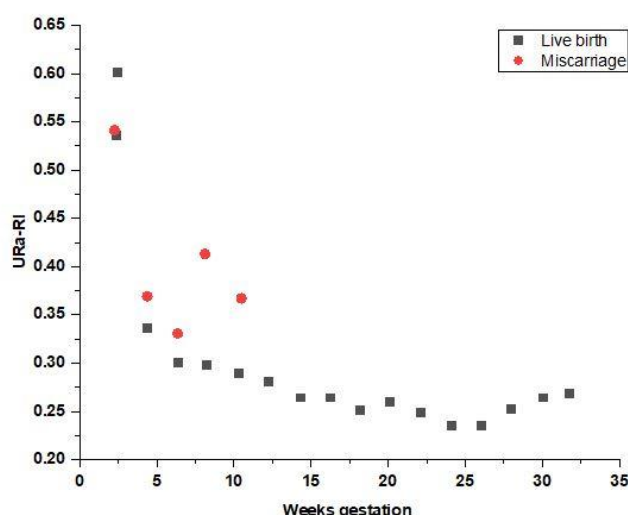


Figure 3: URa-RI levels

The changing pattern of the “uterine radial artery resistance index (URa-RI)” is shown in Figure 3. In most cases, URa-RI levels fell dramatically throughout pregnancy. Women who miscarried at 4 or 6 weeks of pregnancy had greater URa-RI levels than women who gave birth to healthy babies. However, there was no statistically meaningful change. At eight weeks of pregnancy, the rate of miscarriage was substantially greater than in women who delivered a healthy baby. At 10 weeks of pregnancy, there were no notable differences in URa-RI levels between the two groups.

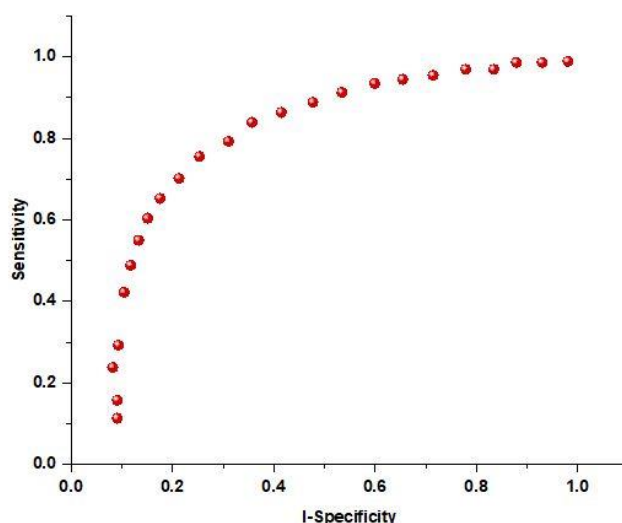


Figure 4: URa-RI level segregation at 12 weeks gestation

ROC curve analysis was utilized to further support the URa-RI level's capacity for segregation at eight weeks gestation. Figure 4 shows that the URa-RI level at eight weeks gestation can identify between women who miscarried and those who delivered a live child with an area under the curve (AUC) of 85.29%. For the URa-RI levels, ROC curve analysis determined that a cutoff point 0.45 had the optimum sensitivity and specificity ratio. The negative predictive value at or below this threshold (i.e., excluding miscarriage) was an astonishing 97.53%.

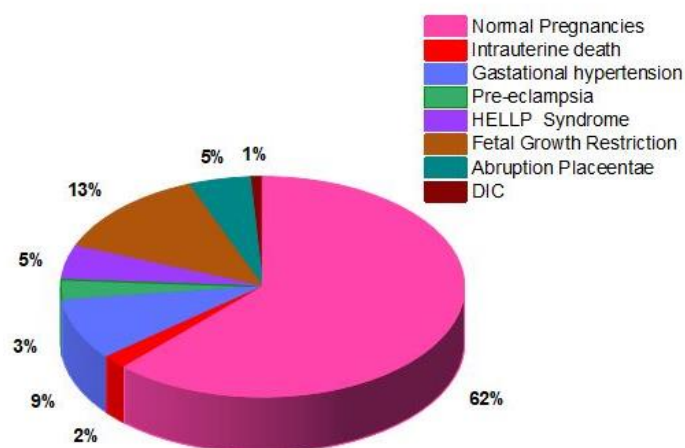


Figure 6: Normal and abnormal prevalence of pregnancies

The term "pregnancy prevalence" describes the frequency or occurrence of pregnancies within a particular population over a defined time frame. While abnormal pregnancy prevalence denotes a larger or lower incidence than generally observed, normal pregnancy prevalence refers to the expected rate of pregnancies in a population. The participants were 459 pregnant women. The following 16 participants were excluded from the study due to their medical conditions: 2 patients with type 1 diabetes, three patients with chronic hypertension, one carrying a fetus with congenital cardiac defects, and ten patients with double or triple thrombophilic patterns. Poor pregnancy outcomes due to fetoplacental insufficiency were separated into two groups among the final study's 284 participants: those who did and did not have "preeclampsia, HELLP syndrome, GH, FGR, ID, abruptio placentae, or DIC." The prevalence of pregnancies is shown in Figure 6, with FGR serving as the series' most expected unfavorable pregnancy outcome.

4. Discussion

Patients with genetic thrombophilia may be at increased risk for complications during pregnancy, including "preeclampsia, intrauterine growth restriction, placental abruption, and multiple miscarriages." Groups II and III are being studied to determine pregnancy outcomes; patients with RPL and genetic thrombophilia were enrolled in the research. The number of live births experienced by each Group was similar. The number of preterm deliveries and incidences of preeclampsia increased in the Group that received only low doses of aspirin. Preeclampsia, placental abruption, and intrauterine growth restriction are all conditions that can arise during pregnancy and may be linked to genetic thrombophilia because of thrombosed microvasculature. Women with RPL and their families often turn to anticoagulant medications as their first line of treatment because thrombophilia may have a role in the condition's pathogenesis [16]. The most effective preventative medication for these patients is still a mystery, as there have been contradictory studies on their efficacy. Many studies showed LMWH's advantages for RPL women; however, they were non-randomized, placebo-controlled, and had methodological faults. Three groups of thrombophilic and RPL-positive women received either aspirin (100 mg/day), enoxaparin (40 mg/day). Neither the rate at which babies were born alive, nor the incidence of complications during pregnancy varied

significantly between the groups in this randomized multicenter study. However, patients with inherited thrombophilia, recently identified kinds of hereditary thrombophilia, and APS were included in this investigation. The distribution of APS patients was unknown due to the variety of the categories. Due to the established advantages of Group III on live birth rates in APS mothers, the study [17] findings may have been affected by APS patients. LMWH and aspirin did not improve obstetric outcomes in RPL and thrombophilia patients in the HepASA Trial. This study had similar live birth rates.

In a recent meta-analysis [18], aspirin users and non-users had comparable live birth rates. In thrombophilic women, aspirin prevented miscarriages. Unlike previous studies, we did not evaluate RPL patients with APS, other inherited thrombophilia, or unknown causes. As other studies have found, LMWH did not increase the live birth rate. Compared to aspirin alone, LMWH does not improve aspirin efficacy. Studies have linked preeclampsia with familial thrombophilia [19]. Research [20] shows that genetic thrombophilia increases preeclampsia risk in pregnant women. Aspirin-treated preeclampsia survivors had reduced rates. This trial's control group was untreated. In a recent meta-analysis, LMWH and low-dose aspirin (100 mg) reduced preeclampsia. LMWH + aspirin or aspirin alone lowered preeclampsia rates compared to aspirin alone. Aspirin prevents preeclampsia in hereditary thrombophilia patients. Aspirin may reduce this consequence in high-risk preeclampsia patients, according to meta-analyses. Aspirin anticoagulant and anti-inflammatory activities may benefit. According to the results, LMWH and aspirin prevents preeclampsia in RPL women with hereditary thrombophilia better than aspirin alone. Additionally, we observed greater preterm birth rates among RPL patients who were only given aspirin. This might be because there are more preeclampsia patients in this Group. All groups experienced frequent other obstetric issues.

5. Conclusion

The live birth rates in women with inherited thrombophilia are the same regardless of which category they fall into (Group I, Group II, or Group III). Preeclampsia risk is reduced in women with genetic thrombophilia after receiving LMWH together with aspirin during pregnancy. Group III may have a higher preventative impact regarding preeclampsia and adverse pregnancy outcome

than Group II, despite not increasing live birth rates or Group I administration. More clinical investigations must be conducted to determine whether group III has any potential advantages for individuals who are already at risk.

The study suffered most from its failure to include a control group of untreated patients. Because Group II's impact on live birth rates and other detrimental obstetric outcomes in RPL patients with hereditary thrombophilia are still unknown, this condition cannot be ruled out as a possible complication. To withhold anticoagulant therapy from women who have been diagnosed with hereditary thrombophilia, however, would be unethical. Additionally, we did not examine the negative effects of Group II and Group III in this trial, such as vaginal bleeding or other bleeding; instead, we compared how Group II and Group III affected pregnancy outcomes.

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