First Trimester Clinical Characteristics and Pregnancy Outcomes in Women with Recurrent Pregnancy Loss

Cristina Trilla *, Judit Platero, Nuria Camprubí, Josefina Mora, Cristina Luna, Daniel Oros, Elisa Llurba

Posted Date: 26 June 2025

doi: 10.20944/preprints202506.2094.v1

Keywords: recurrent pregnancy loss; first trimester; maternal characteristics; biochemical markers; uterine artery pulsatility index; preeclampsia; screening

 doi:10.20944/preprints202506.2094.v1

Article

First Trimester Clinical Characteristics and Pregnancy Outcomes in Women with Recurrent Pregnancy Loss

Cristina Trilla [1,2,3,4,*], Judit Platero [1], Núria Camprubí [1], Josefina Mora [2,5], Cristina Luna [6], Daniel Oros [6] and Elisa Llurba [1,2,3,4]

[1] Department of Obstetrics and Gynecology, Institut d'Investigació Biomèdica Sant Pau - IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[2] Faculty of Medicine, Universitat Autònoma de Barcelona, Spain
[3] Spanish Network in Maternal, Neonatal, Child and Developmental Health Research (RICORS-SAMID, RD24/0013/0001), Instituto de Salud Carlos III, 28040 Madrid, Spain
[4] Women and Perinatal Health Research Group, Institut de Recerca (IR SANT PAU), Sant Quintí 77-79, 08041 Barcelona, Spain
[5] Department of Biochemistry. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[6] Obstetrics Department, Aragon Institute of Health Research (IIS Aragon), Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
* Correspondence: ctrilla@santpau.cat; Tel.: 0034935337041

Abstract

Objective: To describe first-trimester maternal, biochemical, biophysical, and ultrasound characteristics in women with recurrent pregnancy loss (RPL) compared to women without RPL. Methods: Retrospective cohort study analyzing data from 4440 pregnant women, including 142 women with previous RPL. Maternal and pregnancy characteristics, first-trimester biochemical markers, biophysical assessments, early-onset preeclampsia (EOPE) risk and perinatal outcomes were compared. Results: Women with RPL were older (37.8 vs. 34.0 years, $p < 0.001$), had higher rates of antiphospholipid syndrome (4.9% vs. 0.9%, $p<0.001$), other thrombophilias (5.6% vs. 0.8%, $p < 0.001$) and thyroid disorders (14% vs. 7.5%, $p=0.010$) than women without RPL. Uterine artery pulsatility index (UtA-PI) values, pregnancy-associated plasma protein-A (PAPP-A) levels, mean arterial pressure and final risk for EOPE were comparable between groups. However, RPL group had higher rates of very-high risk for PE (10.6 vs 5.1, $p=0.011$). Likewise, second-trimester UtA-PI was higher in this group (1.10 vs. 1.01, $p=0.045$). Aspirin and low molecular weight heparin prophylaxis were more frequent in women with RPL (23.8% vs. 9.6%, $p < 0.001$; 14.7% vs. 0.1%, $p<0.001$). Regarding perinatal outcomes, we found a higher incidence of second trimester intrauterine demise in the RPL group (6.4% vs. 1.4%, $p=0.011$), with no other differences observed in other outcomes. Conclusions: Women with RPL exhibit distinct maternal characteristics and worse pregnancy outcomes, although first-trimester markers do not seem to significantly differ from findings in women without RPL. These findings underscore the importance of tailored screening and intervention protocols to improve perinatal outcomes in this high-risk population.

Keywords: recurrent pregnancy loss; first trimester; maternal characteristics; biochemical markers; uterine artery pulsatility index; preeclampsia; screening

1. Introduction

Spontaneous miscarriage, which occurs in about 15–20% of clinically recognized pregnancies, represents the most prevalent complication during early pregnancy [1]. Recurrent pregnancy loss (RPL) is defined as the loss of two or more consecutive pregnancies before the fetus reaches

 doi:10.20944/preprints202506.2094.v1

viability [2]. RPL affects approximately 3-5% of couples attempting to conceive, and its incidences is particularly high in the first trimester of pregnancy [3,4], posing significant emotional and physical challenges to affected women. While associated etiologies are multifactorial, including gynecological, anatomical, genetical, hormonal, immunological, and environmental factors, many cases remain unexplained despite comprehensive evaluations [5]. This highlights the complexity of miscarriage diagnosis and pregnancy management of women with previous RPL.

Maternal characteristics of women with RPL have been extensively described. Previous studies have identified advanced maternal age, thrombophilia, and autoimmune disorders as significant risk factors for RPL [6]. Women with RPL are also at an increased risk of adverse obstetric outcomes, such as preeclampsia (PE), preterm birth (PTB), and intrauterine growth restriction (IUGR). Recent research has shown that women with a history of RPL are 2-3 times more likely to develop gestational hypertension or preeclampsia, and exhibit a 60% increased risk of PTB, compared to the general obstetric population [7–9]. The pooled odds ratios of these complications seem to progressively increase with increasing number of miscarriages, indicating a dose-response pattern and supporting the presence of a biological gradient [8]. Furthermore, the odds for IUGR are 2 times higher in these women [10], underscoring the potential long-term impact of RPL on maternal and fetal health.

Despite maternal characteristics, obstetric outcomes and long-term health outcomes of women with RPL have been previously described, limited data exist on first-trimester characteristics between women with and without RPL. Miscarriage and placental dysfunctional disorders share, to some extent, the same pathophysiology. Thus, a history of RPL might be associated with an increased risk of PE and placental insufficiency disorders. As the pyramid of care in obstetrics has shifted an improved stratification of risk in first-trimester, understanding these differences is essential for optimizing pregnancy management and maternal and fetal outcomes in women with previous RPL. This study aims to describe the first-trimester maternal, biochemical, biophysical, and ultrasound characteristics of women with RPL compared to women without a history of RPL.

2. Material and Methods

This was a prospective observational cohort study including women with a singleton pregnancy who performed ultrasound follow-ups in the Prenatal Diagnosis Unit of Hospital de la Santa Creu i Sant Pau, between January 2020, and December 2022. Women with a singleton pregnancy and a fetus with a crown-rump length (CRL) ranging from 45 to 84 mm were invited to participate. Women were withdrawn from the study in case of fetal chromosomal or genetic abnormality, or in case of major fetal anomaly diagnosed during pregnancy or at birth. This study is an unplanned subanalysis from a larger research study aimed to determine the effectiveness of a sequential screening strategy for PE in the first trimester. This study was approved by the Ethics Committee of the Institutional Review Board at Hospital de la Santa Creu i Sant Pau and was registered with ClinicalTrials.gov, number NCT04767438.

2.1. Maternal and Pregnancy Characteristics

Baseline maternal characteristics were documented, including age, ethnicity, body mass index (BMI), smoking status, and medical history (diabetes, hypertension, kidney disease, autoimmune and thyroid disorders, and inherited or acquired thrombophilia - antiphospholipid syndrome (APS)-). Women with **two or more** pregnancy losses of a clinically confirmed pregnancy, whether consecutive or not, were classified as women with previous RPL. Additionally, the following pregnancy-related information was recorded: type of conception, parity, use of aspirin or low-molecular-weight heparin (LMWH) during pregnancy, gestational age (GA) at the time of the first-trimester blood analysis, and GA at the time of first and second trimester ultrasounds.

 doi:10.20944/preprints202506.2094.v1

2.2. First-Trimester Variables

First-trimester variables included biochemical and biophysical variables. Among biochemical variables, pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) were assessed. Serum levels of PlGF and PAPP-A were measured using fully automated electrochemiluminescence immunoassays on a Cobas e 601 analyzer (Roche Diagnostics). Multiples of the median (MoM) values for first-trimester UtA-PI, PAPP-A, and PlGF were derived from locally established medians, employing a multivariate Gaussian distribution model validated in our population [11]. However, PlGF analysis was not included in the final analysis since results were only available for 10 women in the RPL group.

Biophysical variables included mean arterial pressure (MAP) and uterine artery pulsatility index (UtA-PI). Systolic (SBP) and diastolic blood pressure (DBP) were measured on the day of the first ultrasound using a calibrated Tensoval Duo Control device (Hartmann AG, Heidenheim, Germany). Blood pressure was recorded once after a brief resting period, with the woman seated, as in our standard clinical practice. MAP was calculated using the formula: MAP = (SBP + 2 × DBP) / 3. UtA-PI was assessed transabdominally during the first and second trimesters using a standardized methodology [12].

2.3. Obstetric Outcomes

First-trimester early-onset PE screening was estimated using a previously described multivariate method including maternal factors, biochemical and biophysical variables [13]. In a first stage of screening, 3 risk groups were defined: if risk is > 1/50 women are identified as very high-risk and aspirin prophylaxis is recommended; if risk is between 1/51 and 1/500 women are defined as intermediate risk and require a second stage of evaluation, and if risk is < 1/501 women are identified as low risk. In a second stage, PlGF is determined in the intermediate risk group, finally stratifying women as low or high risk. Results of this screening were recorded for analysis. Perinatal outcomes including second trimester pregnancy loss (below 28 weeks), stillbirth (above 28 weeks), PE, birthweight, gestational age at delivery and mode of delivery, were also documented.

All maternal and pregnancy characteristics, biochemical and biophysical variables, screening results, and perinatal outcomes were extracted from clinical records. Data were analyzed using descriptive statistics. Continuous variables were expressed as mean (standard deviation) or median (interquartile range) and compared using t-tests or Mann-Whitney U tests, where appropriate. Categorical variables were expressed as frequencies (%) and analyzed using chi-square or Fisher's exact tests. A p-value < 0.05 was considered statistically significant.

3. Results

A total of 4476 women were included in the study. Of those, 36 were withdrawn due to exclusion criteria, leaving a final study population of 4440 women, with 142 of them having a history of RPL (3.2%).

Women with RPL were significantly older (37.8 ± 4.6 vs. 33.9 ± 5.2 years, $p < 0.001$) and had a higher prevalence of antiphospholipid syndrome (4.9% vs. 0.9%, $p < 0.001$), other thrombophilias (5.6% vs. 0.8%, $p < 0.001$), thyroid disorders (14.1% vs. 7.5%, $p = 0.009$), and use of assisted reproductive technologies (16.2% vs. 9.9%, $p = 0.022$), including egg donation. In this study, the rate of nulliparity was higher in women without history of RPL (43% vs. 56.7%, $p = 0.001$). Among obstetric outcomes in previous pregnancies, the rates of previous PTB, PE, IUGR and gestational diabetes were higher in the RPL group, although only differences for gestational diabetes were statistically significant (1.7% vs. 4.2%, $p = 0.042$). These results are summarized in Table 1.

 doi:10.20944/preprints202506.2094.v1

Table 1. Maternal and pregnancy characteristics in women with and without recurrent pregnancy loss.

Maternal and pregnancy characteristics	No recurrent pregnancy loss n=4298	Recurrent pregnancy loss n=142	p
Age (years)	33.9 (5.2)	37.8 (4.6)	< 0.001
BMI (Kg/m^2)	24.2 (4.7)	24.5 (4.6)	0.366
Smoking habit	344 (8)	9 (6.3)	0.635
Ethnic origin			
White	3091 (71.9)	109 (76.8)	
Latin-American	786 (18.3)	18 (12.7)	
Black	67 (1.6)	4 (2.8)	
Asian	107 (2.5)	2 (1.4)	0.396
South-Asian	150 (3.5)	5 (2.5)	
North-African	97 (2.3)	4 (2.8)	
Medical history			
Chronic hypertension	58 (1.3)	1 (0.7)	> 0.999
Diabetes mellitus	43 (1)	1 (0.7)	> 0.999
Renal disease	16 (0.4)	1 (0.7)	0.425
Autoimmune disease	18 (0.4)	2 (1.4)	0.133
Antiphospholipid syndrome	37 (0.9)	7 (4.9)	< 0.001
Other thrombophilia	34 (0.8)	8 (5.6)	< 0.001
Thyroid disorders	323 (7.5)	20 (14.1)	0.009
Assisted reproductive technologies	425 (9.9)	23 (16.2)	0.022
Egg donation	161 (3.7)	12 (8.5)	0.012
Obstetric history			
Nulliparous	2435 (56.7)	61 (43)	0.001
Parous with previous PE	106 (2.5)	6 (4.2)	0.173
Parous with previous SGA	63 (1.5)	5 (3.5)	0.065
Parous with previous GMD	74 (1.7)	6 (4.2)	0.042
Parous with previous PTB	83 (1.9)	4 (2.8)	0.360

Data are expressed as mean (SD) or n (%). BMI: Body mass index; PE: preeclampsia; SGA: small-for-gestational age; GDM: gestational diabetes mellitus; PTB: preterm birth.

Table 2 depicts the results regarding the comparison of first-trimester variables and PE risk assessments between groups. There were no significant differences in biochemical markers such as PAPP-A (1.10 vs. 1.04 MoM, p = 0.691). No differences were found in the first-trimester biophysical variables included in the study. There were no statistical differences in the final high-risk rate for early-onset PE, although this rate was higher in the RPL group (13.4% vs 9.5%, p = 0.146). However, the rate of women with a very high-risk of PE (>1/50) was significantly higher in the RPL group (10.6% vs 5.1%, p=0.011). Regarding second trimester UtA-PI, results showed a significantly higher UtA-PI

 doi:10.20944/preprints202506.2094.v1

in women with RPL (1.10 vs. 1.01, p = 0.045). Women with RPL were more likely to receive aspirin (23.9% vs. 9.5%, p < 0.001) and LMWH (14.8% vs. 0.1%, p < 0.001) prophylaxis during pregnancy.

Table 2. Comparison of pregnancy characteristics between women with and without recurrent pregnancy loss.

Pregnancy characteristics	No recurrent pregnancy loss n=4298	Recurrent pregnancy loss n=142	p
Biochemical markers			
GA at blood test	10.8 (1.1)	10.7 (1.0)	0.402
PAPP-A (MoM)	1.04 (0.73-1.50)	1.10 (0.73-1.53)	0.691
MAP (MoM)	1.03 (0.9-1.0)	1.03 (0.9-1.1)	0.809
First trimester ultrasound			
GA at ultrasound	12.8 (0.6)	12.8 (0.5)	0.321
UtA-PI	1.64 (0.4)	1.66 (0.5)	0.516
UtA-PI (MoM)	1.04 (0.87-1.23)	1.06 (0.86-1.28)	0.696
Second trimester ultrasound			
GA at ultrasound	20.8 (0.7)	20.7 (0.6)	0.184
UtA-PI	1.01 (0.3)	1.10 (0.4)	0.045
UtA-PI > 95th centile	170(4.2)	8 (6.3)	0.257
Screening for early-onset PE			
Very high-risk	220 (5.1)	15 (10.6)	0.011
Final high-risk	409 (9.5)	19 (13.4)	0.146
Prophylactic treatments			
Aspirin	410 (9.5)	34 (23.9)	< 0.001
LMWH	3 (0.1)	21 (14.8)	< 0.001

Data are expressed as mean (SD), n (%) or median (IQR). MoM: multiples of the median; GA: gestational age; PAPP-A: pregnancy-associated plasma protein-A; MAP: mean arterial pression; UtA-PI: uterine artery pulsatility index; PE: preeclampsia; LMWH: Low molecular weight heparin.

Perinatal results were available for 3902 participants (87.9%). Pregnancy outcomes were similar between groups, with no significant differences in birth weight, overall PE rates (4.8% vs. 4.5%, p = 0.824), or cesarean delivery rates (28% vs. 24.8%, p = 0.449). However, women with RPL had a significantly higher rate of second trimester intrauterine fetal demise (6.4% vs. 1.4%, p=0.001). Among those cases, mean GA at demise was 17.3 (3.1) weeks. There were 11 cases of severe IUGR before 22 weeks. Only 4 of the cases ending in second trimester pregnancy loss had a first-trimester high-risk result at the PE screening. Prophylactic aspirin had been prescribed in 5 cases, with one patient also taking LMWH. Finally, women with RPL delivered one week earlier than women without a history of RPL, although this difference did not reach statistical significance. There results are presented in Table 3.

Table 3. Comparison of perinatal outcomes in women with and without recurrent pregnancy loss.

Pregnancy outcome	No recurrent pregnancy loss n=3777	Recurrent pregnancy loss n=125	*p*
Second trimester miscarriage	53 (1.4)	8 (6.4)	0.001
Stillbirth	10 (0.3)	0 (0)	> 0.999

 doi:10.20944/preprints202506.2094.v1

Fetal sex			
Male	1950 (51.9)	69 (56.6)	0.357
Female	1806 (48.1)	53 (43.4)	
Birth weight (grams)	3248 (543)	3271 (551)	0.641
Overall PE	168 (4.5)	6 (4.8)	0.824
Early-onset PE	16 (0.4)	0 (0)	> 0.999
Preterm PE	35 (0.9)	1 (0.8)	> 0.999
Term PE	134 (3.5)	5 (4)	0.804
GA at birth	39.2 (3.2)	38.2 (6.0)	0.069
Cesarean delivery	925 (24.8)	33 (28)	0.449

Data are expressed as mean (SD) or n (%). PE: preeclampsia; GA: gestational age.

4. Discussion

This study results highlight significant differences in maternal characteristics and pregnancy outcomes between women with and without RPL. Despite no significant differences were found in the first-trimester biochemical and biophysical variables analyzed, women with RPL exhibit higher rates of very-high risk of early-onset PE and higher rates of second trimester uterine demise, underscoring the need for tailored obstetric care in this population.

Our study confirmed several associations between maternal factors and RPL. For instance, women with RPL had a more advanced maternal age and a higher prevalence of thrombophilia and thyroid disorders. This is consistent with previous literature and underscores advanced maternal age as a significant risk factor for both miscarriage and poor obstetric outcomes [14,15]. Age-related decline in oocyte quality and increased aneuploidy rates likely contribute to these outcomes [16]. However, even after excluding pregnancies with confirmed chromosomal or genetic abnormalities, the rate of intrauterine demise remained higher in women with previous RPL. This finding suggests that other factors may play a critical role in the pathophysiology of pregnancy loss in women with RPL beyond the first trimester, highlighting the need for a structured and comprehensive evaluation in this population.

We found a strong association of APS and other thrombophilia with RPL, which also aligns with previous evidence [17]. APS is one of the most well-documented causes of RPL, with multiple studies confirming its role in pregnancy loss through placental vascular dysfunction [18]. Consistently with these findings, the use of aspirin and LMWH prophylaxis was significantly higher in the RPL group. These therapies have been shown to improve live birth rates in APS women, by preventing antiphospholipid antibodies from binding to the trophoblast, preventing complement activation, promoting trophoblastic invasiveness and mitigating placental thrombotic events [19]. However, treatment rates with aspirin or LMWH in our study were higher than expected and cannot be attributed to maternal risk factors or preeclampsia screening alone. This corroborates a widespread use of prophylaxis treatments in women with RPL in clinical practice. However, while these interventions are widely recommended, their efficacy in improving outcomes in women with unexplained RPL is highly controversial and remains a topic of ongoing research [20,21].

Similarly, we found a higher prevalence of thyroid disorders in the RPL cohort. This reinforces the importance of thyroid function screening in this population. Subclinical hypothyroidism and thyroid autoimmunity are recognized contributors to miscarriage, likely due to impaired endometrial receptivity [22,23]. Our findings highlight the necessity of optimizing thyroid function preconceptionally and during early pregnancy to improve outcomes.

Regarding the first-trimester variables included in PE screening, our results showed comparable levels of PAPP-A between groups. This contrasts with some prior studies suggesting these markers as potential predictors of adverse pregnancy outcomes [24,25]. No further differences were neither observed in UAt-PI and, consequently, final rates of high-risk for PE were comparable between

 doi:10.20944/preprints202506.2094.v1

groups. However, RPL is not a maternal factor included in any of the multivariate systems that have been proposed to screen for PE. In our study, women with prior RPL had significantly higher rates of very-high risk of PE and higher UtA-PI in the second trimester. This suggests that this population should be considered at a higher risk for adverse outcomes regardless of first-trimester results. The clinical usefulness of additional biomarkers regarding endometrial receptivity, inflammation, placental function and maternal immune response should be investigated [25].

The association between RPL and subsequent adverse pregnancy outcomes is a subject of ongoing research and debate. Some studies have identified a significant correlation between RPL and increased risks of complications such as pre-eclampsia, preterm birth, and small-for-gestational-age infants [26]. Conversely, other research has suggested that, many women with a history of RPL can experience successful pregnancies without significant complications [27,28]. These conflicting findings indicate that, while there is evidence supporting an increased risk of adverse outcomes in women with RPL, the magnitude of this risk may vary depending on individual circumstances and obstetric care.

The higher rate of intrauterine fetal demise in women with RPL found in our study is particularly concerning. This indicates that pregnancy risk in women with RPL extends beyond the first trimester. This underscores the need for advanced monitoring and tailored care throughout pregnancy in this population. Increased antenatal surveillance including serial assessments of placental function, fetal growth and well-being may be beneficial in mitigating these risks. Likewise, understanding the underlying cause of miscarriage may lead to early interventions and improved outcomes.

This study's strengths include its prospective design and the use of multivariate screening for identifying high-risk pregnancies, ensuring robust and clinically relevant findings. Another significant strength is the comprehensive assessment of maternal, biochemical, biophysical, and ultrasound parameters in the first-trimester. To the best of our knowledge, this is the first time that first-trimester characteristics of women with previous RPL are assessed. However, several limitations must also be acknowledged. First, the heterogeneity of the RPL group, encompassing various etiologies and treatment regimens, complicates direct comparisons and necessitates cautious interpretation of results. Additionally, the relatively small sample size of the RPL group limits the generalizability of findings. Finally, despite a higher rate of intrauterine demise in the RPL groups, no other differences in maternal or neonatal outcomes were observed. That could be secondary to the higher proportion of parous women in the RPL group or to the widespread use of prophylactic treatment. Prospective studies aiming to clarify this are necessary.

In conclusion, our study contributes to the growing body of evidence on RPL by characterizing the first trimester clinical profile of these women. Our findings support that women with previous RPL exhibit distinct maternal characteristics and are also at higher risk for intrauterine demise, despite no significant differences were found in first-trimester markers currently used in clinical practice. This underscores the need for intensified surveillance and tailored management strategies for this high-risk population until delivery, not until first trimester viability. Multidisciplinary care involving maternal-fetal medicine specialists, hematologists, immunologists and reproductive endocrinologists is essential to optimize outcomes.

Author Contributions: Conceptualization, Cristina Trilla and Elisa Llurba. Methodology, Cristina Trilla and Daniel Oros. Formal Analysis, Cristina Trilla, Judit Platero. Investigation, Cristina Trilla, Josefina Mora and Cristina Luna. Data Curation, Judit Platero, Nuria Camprubí, Josefina Mora. Writing – Original Draft Preparation, Cristina Trilla. Writing – Review & Editing, Elisa Llurba, Daniel Oros. Funding Acquisition, Daniel Oros.

Acknowledgments: This study (PI19/692) was supported by the government of Spain, Plan Estatal de I+D+I and Instituto de Salud Carlos III- Subdirección General de Evaluación y Fomento de la Investigación Sanitaria, project PI19/00692, the European Regional Development Fund (FEDER), and by the Spanish Network in Maternal, Neonatal, Child and Developmental Health Research (RICORS-SAMID, RD24/0013/0001), Instituto de

 doi:10.20944/preprints202506.2094.v1

Salud Carlos III, Madrid, Spain, funded by the Recovery, Transformation and Resilience Plan 2017–2020, ISCIII, and by the European Union—Next Generation EU.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Jauniaux E, Burton GJ. Pathophysiology of histological changes in early pregnancy loss. Placenta. 2005;26:114–23.
2. Regan L, Rai R, Saravelos S, Li T, Gynaecologists the RC of O and. Recurrent MiscarriageGreen-top Guideline No. 17. BJOG: Int J Obstet Gynaecol. 2023;130(12):e9–39.
3. ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Nelen W, Peramo B, Quenby S, Vermeulen N, Goddijn M. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open. 2018;2018(2):hoy004.
4. Dimitriadis E, Menkhorst E, Saito S, Kutteh WH, Brosens JJ. Recurrent pregnancy loss. Nat Rev Dis Primers. 2020;6(1):98.
5. Habets DHJ, Schiffer VMMM, Kraneburg LPA, de Krom FJW, Gürtekin I, van Bree BE, van Golde RJT, Wieten L, Spaanderman MEA, Al-Nasiry S. Preconceptional evaluation of women with recurrent pregnancy loss: the additional value of assessing vascular and metabolic status. BMC Pregnancy Childbirth 2022;22(1):75.
6. Turesheva A, Aimagambetova G, Ukybassova T, Marat A, Kanabekova P, Kaldygulova L, Amanzholkyzy A, Ryzhkova S, Nogay A, Khamidullina Z, Ilmaliyeva A, Almawi WY, Atageldiyeva K. Recurrent Pregnancy Loss Etiology, Risk Factors, Diagnosis, and Management. Fresh Look into a Full Box. J Clin Med. 2023;12(12):4074.
7. Gunnarsdottir J, Stephansson O, Cnattingius S, Akerud H, Wikström AK. Risk of placental dysfunction disorders after prior miscarriages: a population-based study. Am J Obstet Gynecol. 2014;211(1):34.e1-8.
8. Bhattacharya S, McCall SJ, Woolner AMF. Recurrent pregnancy loss and subsequent preterm birth: association or causation? Fertil Steril. 2022;117(4):820-821.
9. Hautamäki H, Gissler M, Heikkinen-Eloranta J, Tiitinen A, Peuranpää P. Pregnancy and perinatal outcomes in women with recurrent pregnancy loss-A case-control study. Acta Obstet Gynecol Scand. 2025;104(2):368-379.
10. Ausbeck E, Blanchard C, Neely C, Tita A, Szychowski J, Harper L. Perinatal outcomes in women with a history of recurrent pregnancy loss. Am J Obstet Gynecol. 2019; 220 (1), S118.
11. Serra B, Mendoza M, Scazzocchio E, Meler E, Nolla M, Sabrià E, Rodríguez I, Carreras E. A new model for screening for early-onset preeclampsia. Am J Obstet Gynecol. 2020;222(6):608.e1-608.e18.
12. Gomez O, Figueras F, Fernandez S, Bennasar M, Martinez JM, Puerto B, Gratacós E. Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation. Ultrasound Obstet Gynecol. 2008;32(2):128–32.
13. Trilla C, Mora J, Ginjaume N, Nan MN, Alejos O, Domínguez C, Vega C, Godínez Y, Cruz-Lemini M, Parra J, Llurba E. Reduction in Preterm Preeclampsia after Contingent First-Trimester Screening and Aspirin Prophylaxis in a Routine Care Setting. Diagnostics. 2022;12(8):1814.
14. Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ. 2019;364:l869.
15. Frick AP. Advanced maternal age and adverse pregnancy outcomes. Best Pract Res Clin Obstet Gynaecol. 2021;70:92-100.
16. Mikwar M, MacFarlane AJ, Marchetti F. Mechanisms of oocyte aneuploidy associated with advanced maternal age. Mutat Res Rev Mutat Res. 2020;785:108320.
17. Santos TDS, Ieque AL, de Carvalho HC, Sell AM, Lonardoni MVC, Demarchi IG, de Lima Neto QA, Teixeira JJV. Antiphospholipid syndrome and recurrent miscarriage: A systematic review and meta-analysis. J Reprod Immunol. 2017;123:78-87.
18. Alijotas-Reig J, Esteve-Valverde E, Anunciación-Llunell A, Marques-Soares J, Pardos-Gea J, Miró-Mur F. Pathogenesis, Diagnosis and Management of Obstetric Antiphospholipid Syndrome: A Comprehensive Review. J Clin Med. 2022;11(3):675.
19. El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet PE. Recurrent pregnancy loss: current perspectives. Int J Womens Health. 2017;9:331-345.

 doi:10.20944/preprints202506.2094.v1

20. de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. Cochrane Database Syst Rev. 2014;2014(7):CD004734.
21. Yan X, Wang D, Yan P, Li H. Low molecular weight heparin or LMWH plus aspirin in the treatment of unexplained recurrent miscarriage with negative antiphospholipid antibodies: A meta-analysis of randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2022;268:22-30.
22. Liu H, Shan Z, Li C, Mao J, Xie X, Wang W, Fan C, Wang H, Zhang H, Han C, Wang X, Liu X, Fan Y, Bao S, Teng W. Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. Thyroid. 2014;24(11):1642-9.
23. Wu Z, Cai Y, Xia Q, Liu T, Yang H, Wang F, Wang N, Yu Z, Yin C, Wang Q, Zhu D. Hashimoto's thyroiditis impairs embryo implantation by compromising endometrial morphology and receptivity markers in euthyroid mice. Reprod Biol Endocrinol. 2019;17(1):94.
24. Sovio U, Gaccioli F, Cook E, Charnock-Jones DS, Smith GCS. Association between adverse pregnancy outcome and placental biomarkers in the first trimester: A prospective cohort study. BJOG. 2024;131(6):823-831.
25. Luo, Y., Zhou, Y. Identification of novel biomarkers and immune infiltration features of recurrent pregnancy loss by machine learning. Sci Rep. 2023;13,10751.
26. Rasmark Roepke E, Christiansen OB, Källén K, Hansson SR. Women with a History of Recurrent Pregnancy Loss Are a High-Risk Population for Adverse Obstetrical Outcome: A Retrospective Cohort Study. *J Clin Med*. 2021; 10(2):179.
27. Mohamedain A, Rayis DA, AlHabardi N, Adam I. Association between previous spontaneous abortion and preeclampsia: a case-control study. BMC Pregnancy Childbirth. 2022;22(1):715.
28. Clark K, Barton JR, Istwan N, Rhea D, Desch C, Sibai A, Sibai BM. PP179. The influence of prior abortion on rates of gestational hypertension/pre-eclampsia and spontaneous preterm delivery in nulliparous women. Pregnancy Hypertens. 2012;2(3):337.