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Wiley Blackwell
2025-02

Hautamäki, H, Gissler, M, Heikkinen-Eloranta, J, Tiitinen, A & Peuranpää, P 2025, 'Pregnancy and perinatal outcomes in women with recurrent pregnancy loss-A case-control study', Acta Obstetricia et Gynecologica Scandinavica, vol. 104, no. 2, pp. 368-379. https://doi.org/10.1111/aogs.150

http://hdl.handle.net/10138/591044
10.1111/aogs.15039

Received: 25 September 2024 | Revised: 15 November 2024 | Accepted: 5 December 2024

DOI: 10.1111/aogs.15039

ORIGINAL RESEARCH

Pregnancy and perinatal outcomes in women with recurrent pregnancy loss—A case–control study

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Funding information
Government's Research Financing Government Research Funding Helsinki University Hospital Finnish Government science grant the State Subsidy to Hospitals, Grant/Award Number: TYH2020207 and TYH2024329; Juhani Aho Foundation for Medical Research; The Finnish Cultural Foundation, Grant/Award Number: 00220291; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation, Grant/Award Number: 20217404

Abstract

Introduction: Recurrent pregnancy loss (RPL), defined as two or more pregnancy losses, might be associated with elevated obstetrical and perinatal risks in the following pregnancies. RPL and pregnancy problems related to placental development may have similar etiological features. This study explores the incidences of pregnancy and perinatal outcomes in women with RPL.

Material and Methods: This retrospective case–control study investigated the outcomes of the next subsequent singleton pregnancy after thorough RPL examination ($n=360$) in Helsinki University Hospital, Finland, in 2007–2016. Data for cases and four control women for each case, matched for age, parity, delivery month, year, and hospital ($n=1440$), were retrieved from the Medical Birth Register. Primary outcomes were pregnancy and delivery complications, perinatal outcomes, and characteristics of pregnancy follow-up. Secondary outcomes were maternal and neonatal diagnoses. Associations between RPL and outcomes were estimated with risk ratios with 95% confidence intervals (CI). In sub-analyses, we compared the outcomes of secondary RPL with multipara controls and women with unexplained or explained RPL.

Results: Women with RPL had a higher risk for gestational hypertension (3.1% vs. 1.4%, risk ratio [RR] 2.20 [Confidence interval (CI) 1.06–4.55], $p=0.03$), preterm birth (8.9% vs. 5.8%, RR 1.54 [CI 1.04–2.28], $p=0.04$), malpresentation of the fetus (3.3% vs. 1.5%, RR 2.18 [CI 1.09–4.37], $p=0.02$), premature rupture of membranes (5.6% vs. 2.4%, RR 2.35 [CI 1.37–4.04], $p=0.002$), and had more prenatal visits than controls. Mode of delivery was comparable between the study groups, although RPL women had more induced labor (28.1% vs. 22.2%, RR 1.26 [CI 1.04–1.53], $p=0.02$). Mean birthweight was lower (3387 ± 680 g) in RPL women's newborns than in the control group (3482 ± 564 g, $p=0.02$), and the risk of umbilical artery pH <7.10 (6.7% vs. 3.6%, RR 1.85 [CI 1.15–2.95], $p=0.03$) was higher. Risk ratio for small for gestational age

Abbreviations: BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; ICD-10, 10th Revision of International Statistical Classification of Diseases and Related Health Problems; MBR, Medical Birth Register; PROM, premature rupture of the membranes; RPL, recurrent pregnancy loss; SD, standard deviation; SGA, small for gestational age.

was higher in the secondary RPL group than in multipara controls (5.1% vs. 2.0%, RR 2.50 [CI 1.15–5.42], $p = 0.02$).

Conclusions: Women with a history of RPL seem to have higher risks in their subsequent pregnancies and should therefore be monitored carefully. These findings support the theory of placental development being the common nominator behind hypertensive pregnancy disorders and RPL.

KEYWORDS
perinatal and neonatal diagnoses, perinatal outcome, placental problems, pregnancy outcome, recurrent pregnancy loss, risk pregnancy, subsequent pregnancy

1 | INTRODUCTION

Recurrent pregnancy loss (RPL), defined as two or more pregnancy losses, is a very distressing reproductive problem concerning 2%–3% of couples wishing for a child.[1] Often a history of RPL lays a shadow of worry over the subsequent pregnancy. Therefore, these families need tender loving care—not only during the pregnancy attempts but also during the following pregnancy.[2] They might require additional supportive counseling and intensive follow-up throughout their pregnancies.

Etiology of RPL remains unexplained in over 50% of couples after thorough examinations, which adds to the psychological burden of this condition. Known background factors include hypothyroidism, antiphospholipid syndrome, cervical insufficiency, some uterine anomalies, maternal age, and abnormal parental karyotype.[1] Recent research around etiology of RPL has focused on the formation of the placenta where immunology of early pregnancy seems to play a significant role.[3,4] The correct formulation of the spiral arteries during the first half of the pregnancy is essential to normal function of the placenta and furthermore to a healthy pregnancy.[5] Disturbances in placental development can result in hypertensive placental disorders[6] which in turn might cause preterm births and related perinatal complications.[7] Immunological mechanisms inducing and maintaining maternal tolerance have been found to be similar between RPL and placenta-originated pregnancy problems, which has led to suggestion of them being either parts of the same disease spectrum or a continuum of pregnancy complications.[8,9]

Previous studies have shown increased risk of placental dysfunction-related disorders such as preterm birth[10–13] and preeclampsia[14–16] in women with RPL, but findings are not congruent.[17,18] Also, lower birthweight,[12,13] gestational diabetes (GDM),[10,17] and perinatal death[11] have been associated with a history of pregnancy losses. However, these study designs were mostly either large, population-based birth cohorts that do not investigate women with diagnosed RPL or studies on a small group of selected patients[18,19] and the number of previous pregnancy losses varies. The RPL definition ranges from two to three consecutive or non-consecutive pregnancy losses depending on the source used.[20–22]

We studied the obstetric and perinatal outcomes in subsequent pregnancies of women with examined and diagnosed RPL. We combined information about the couples' previous pregnancies, RPL examinations, etiology, and lifestyle from the hospital records and the Finnish Medical Birth Register (MBR) and compared this cohort to matched controls. We also investigated whether women with RPL need more support during pregnancy, have a diagnosis for fear of childbirth, or underwent elective cesarean delivery more often than control women (Figure 1).

Key points

History of recurrent pregnancy loss is associated with greater risks for hypertensive pregnancy disorders, placental problems, and preterm birth in the subsequent pregnancy. These pregnancies require careful follow-up and support.

2 | MATERIAL AND METHODS

2.1 | Study population

The study population comprises couples referred to Helsinki University Hospital, Helsinki, Finland, for RPL between 2007 and 2016 ($n = 506$). This study examines the first pregnancy after RPL investigations ending in a singleton birth (index pregnancy, $n = 360$). As controls for each RPL woman, four women were selected from MBR and matched for age, parity, year, month, and the hospital of the delivery ($n = 1440$). For sub-analyses, control women with RPL were excluded (three or more miscarriages, $n = 27$). We retrieved comprehensive data about RPL and control women's pregnancies, deliveries, perinatal outcomes, and mothers' and children's perinatal diagnoses according to the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) from the MBR until December 31, 2019. These data were collected concerning all women's index pregnancies and the RPL women's previous pregnancies. All deliveries took place in the Finnish public healthcare system's hospitals. MBR is managed by the Finnish Institute for Health and Welfare. Personal identity numbers

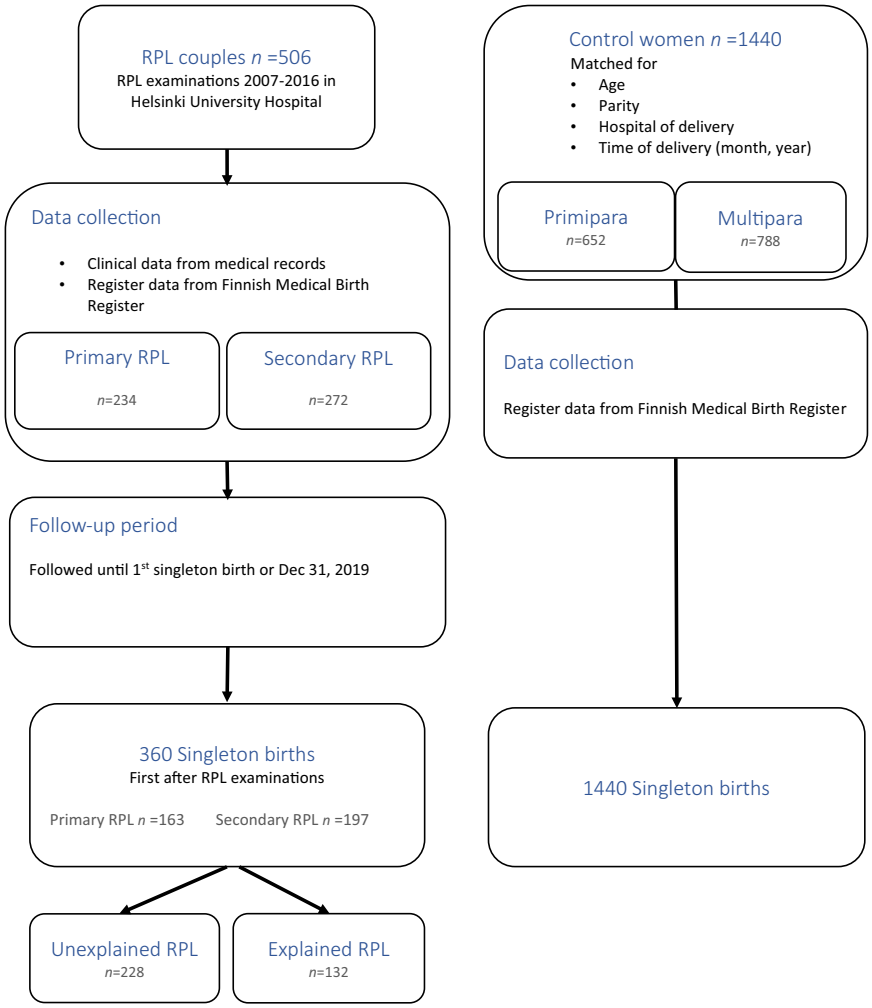

FIGURE 1 Flow chart of the case–control study about recurrent pregnancy loss (RPL) women's subsequent pregnancies.

(anonymized in the process) of all Finnish citizens and permanent residents enable the gathering and linkage of clinical and register data, which was conducted by the Finnish Social and Health Data Permit Authority Findata, which manages the secondary use of social and health care data in Finland.

Of couples with RPL, clinical data of pregnancy history and results of RPL investigations were collected from medical records, as described previously in detail.[23] Shortly, most couples were studied after three or more consecutive clinical first-trimester pregnancy losses or two or more losses with at least one of them between gestational weeks 12+1 and 21+6 when the woman's age was less than 42 years. All met the European Society of Human Reproduction and Embryology's definition for RPL.[20]

We considered RPL explained if the woman's age was ≥40 years, her body mass index (BMI) was ≥30 kg/m^2, or chromosomal abnormality of either parent, uterine abnormality,[24] antiphospholipid syndrome,[25] or polycystic ovary syndrome[26] was diagnosed, or if other test results were abnormal (fasting glucose, thyroid stimulating hormone, thyroid peroxidase antibodies, prolactin, and sperm DNA fragmentation index >30%). On the contrary, RPL was considered unexplained if all results of the assessments were normal. RPL was considered secondary if the woman had children before RPL investigations (Figure 1).

2.2 | Outcome variables

Our primary outcomes were pregnancy and delivery complications, perinatal outcomes, and characteristics of pregnancy follow-up. Secondary outcomes were maternal and neonatal diagnoses.

Live birth was defined as a child born alive and stillbirth as a stillborn child ≥22+0 weeks or birthweight ≥500 g. The birth was considered preterm when occurring before 37+0 and post-term at or after 42+0 gestational weeks. Small for gestational age (SGA, birthweight below −2 SDs in Finnish growth curves) and large for gestational age (birthweight over +2 SDs or >4500 g) with unknown etiology (e.g., congenital malformation syndrome or chromosomal defects) were defined according to Finnish population-based birth size references from MBR.[27] Gestational age was estimated from the last menstrual period and changed accordingly after ultrasound examination for nuchal translucency if difference was more than ±5 days.

Hypertensive diseases of pregnancy, GDM, hepatosis, and other conditions originating during pregnancy were diagnosed and recorded by a physician during pregnancy or at delivery. Gestational hypertension is defined as an elevation of previously normal blood pressure after 20 weeks of gestation over 140 mmHg systolic or 90 mmHg diastolic, without proteinuria. Preeclampsia is diagnosed by newly onset hypertension after 20 gestational weeks

(≥140 mmHg systolic or ≥90 mmHg diastolic blood pressure) and proteinuria (>300 mg/24 h or positive dipstick test in two consecutive measurements). Use of heparin or low-molecular-weight heparin for thrombosis prophylaxis during pregnancy is retrieved from MBR.

Screening for GDM is risk factor based and prior to 2008 criteria were as follows: BMI >25 kg/m^2, age ≤40, glucosuria, prior GDM, and prior macrosomic infant (birthweight >4500 g). Since 2008, all women were screened, except those with the lowest risk (primiparous: age < 25, BMI 18.5–24.9 kg/m^2, and no first-degree relative with type 2 diabetes; multiparous: age <40, BMI <25 kg/m^2, no prior GDM, and no prior macrosomic infant). Oral glucose tolerance test (75 g) is performed at 24–28 gestation weeks. High-risk women (BMI ≥35 kg/m^2, glucosuria, prior GDM, first- or second-degree relative with type 2 diabetes, use of oral corticosteroids, and polycystic ovary syndrome) are screened already at 12–16 weeks. Before 2008, the diagnostic glycemic thresholds were as follows: fasting ≥5.1, 1 h≥10.0, 2 h≥8.7 mmol/L, and ≥2 pathological values needed for diagnosis. From 2008 onwards, one or more pathological values over the threshold were diagnostic, and the thresholds were as follows: fasting ≥5.3, 1 h≥10.0, and 2 h≥8.6 mmol/L. Only insulin treatments that started during pregnancy are recorded in MBR.

We formed three composite outcome variables. *Placental problems* include ICD-10 diagnoses O43 placental disorders, O44 placenta previa, O45 placental abruption, or manual removal of the placenta. *Neonatal composite* outcome consists of the following outcomes: Apgar 5-min points 0–6, umbilical artery pH <7.10, neonatal intensive care unit admission, or perinatal death. For the *prematurity composite outcome*, the following variables were combined: SGA, premature birth <37 gestational weeks, diagnoses of P07 disorders related to short gestation and low birthweight, O42 premature rupture of membranes (PROM), or O10-O14 hypertensive disorders of pregnancy.

2.3 | Statistical analyses

We used χ^2 test for independence to measure differences in incidence of outcomes between RPL and control women and *T* test or Mann–Whitney *U* test to compare the groups. We calculated risk ratios (RR) with 95% confidence intervals (CI) for all outcomes. We used logistic regression to estimate odds ratios for GDM, adjusted with maternal BMI. A significance level of <0.05 was used in all analyses. Outcomes with less than five cases per cell are not reported due to data protection rules. This applies also to risk ratios in case the exact number of cases can be calculated. We analyzed the pseudonymized data with SAS 9.4 and IBM SPSS Statistics 27.

3 | RESULTS

Of the 506 women examined for RPL, 360 (71.1%) had a singleton birth, 45.3% ($n=163$) after primary RPL, and 54.7% ($n=197$) after secondary RPL. In 63.3% (228/360) of women, RPL remained unexplained, whereas in 36.7% ($n=132$), RPL was considered explained.

The control women delivered 1440 singletons. The demographic features and lifestyle factors (BMI and smoking) of the study groups from MBR were comparable, except RPL women were more often divorced, single, or widows (4.4% vs. 2.4%, $p<0.001$), and the index pregnancy was started with medically assisted reproduction (13.1% vs. 9.9%, $p=0.01$) (Table 1). RPL women's mean BMI was similar at the time of examinations (24.4 ± 4.4 kg/m^2) and in early pregnancy (24.4 ± 4.4 kg/m^2).

In their obstetric history (Table 2), RPL women had more ectopic pregnancies (4.4% in RPL vs. 1.1%, $p<0.001$) and induced abortions (13.6% vs. 10.8%, $p=0.004$) than controls. The percentages of previous cesarean sections were 10.6% in RPL women and 13.1% in controls ($p>0.05$).

3.1 | Pregnancy

Women with RPL had more often gestational hypertension than controls (3.1% vs. 1.4%, RR 2.20 [95% CI: 1.06–4.55]); however, the incidence of preeclampsia was comparable between the groups (Table 5). Glucose tolerance test was assessed in 234 (65.0%) RPL women and 868 (60.3%) controls. RPL women were diagnosed with GDM more often than controls (17.2% vs. 12.8%, RR 1.42 [95% CI: 1.04–1.95]), but after adjusting with BMI, the result became non-significant (OR 1.33 [95% CI: 0.95–1.08]). Ten (2.8%) RPL women and 45 (3.1%) control women started insulin therapy. RPL women used low-molecular-weight heparin prophylaxis for thromboembolism more often (9.4% vs. 2.4%, $p<0.001$) than the controls.

Throughout the pregnancy, women with RPL had more visits to public maternity (16.2 ± 4.8 vs. 14 ± 3.9, $p<0.001$) and hospital obstetric (4.7 ± 3.6 vs. 3.4 ± 2.5, $p<0.001$) outpatient clinics than control women. Diagnosis of fear of childbirth (O99.80 in the Finnish ICD-10 classification) was set on 10.0% of RPL women and 7.0% of controls ($p=0.056$).

3.2 | Delivery and postpartum

Delivery outcomes are presented in Table 3. Preterm birth was more common in RPL than in control women (8.9% vs. 5.8% RR 1.54 [95% CI: 1.04–2.28], respectively). Mode of delivery was comparable between the groups, although the labor was induced significantly more often in RPL women, and they delivered by urgent or emergency cesarean more often than controls (16.1% vs. 12.3%, $p>0.05$). Risk for malpresentation of the fetus (RR 2.18 [95% CI: 1.09–4.37]) and PROM (RR 2.35 [95% CI: 1.37–4.04]) was higher in women with RPL compared with control women. The incidence of *placental problems composite* was higher in RPL women, and their placenta was manually removed more often than in control women.

Women with RPL stayed longer in hospital for delivery and puerperium (3.9 ± 5.0 days) than controls (3.3 ± 2.0 days, $p=0.04$). Both groups used labor pain relief methods similarly (data not shown).

TABLE 1 Demographic characteristics of women with recurrent pregnancy loss (RPL) and controls at the time of the index birth.

	RPL women $n=360$		Controls $n=1440$		
	n	(%)	*n*	(%)	*p* Value
Age (year), matching criteria					1.00
<25	15	(4.2)	60	(4.2)	
25–29	51	(14.2)	204	(14.2)	
30–34	129	(35.8)	516	(35.8)	
35–39	121	(33.6)	484	(33.6)	
≥40	44	(12.2)	176	(12.2)	
Mean age (year), mean (SD)	34.4	(4.85)	34.4	(4.84)	1.00
Marital status					**<0.001**
Married, registered partnership or cohabitation	342	(95.0)	1399	(97.2)	
Single, divorced or widow	16	(4.4)	35	(2.4)	
Socio-economic status					0.09
Upper white-collar worker	81	(22.5)	258	(17.9)	
Lower white-collar worker	60	(16.7)	265	(18.4)	
Blue-collar worker	12	(3.3)	80	(5.6)	
Other	21	(5.8)	78	(5.4)	
Unknown	186	(51.7)	759	(52.7)	
Body mass index (kg/m^2) in early pregnancy, mean (SD)	24.43	(4.43)	24.09	(4.65)	0.19
Categorised					0.49
<20	47	(13.1)	201	(14.0)	
20–24.9	179	(49.7)	769	(53.4)	
25–29.9	82	(22.8)	282	(19.6)	
≥30	45	(12.5)	154	(10.7)	
Unknown	7	(1.9)	34	(2.4)	
Smoking during pregnancy					0.34
No	325	(90.3)	1261	(87.6)	
Stopped during 1. trimester	8	(2.2)	60	(4.2)	
Continued	17	(4.7)	78	(5.4)	
Unknown	10	(2.8)	41	(2.8)	
Medically Assisted Reproduction					**0.01**
IVF treatment	13	(3.6)	18	(1.3)	
Insemination	5	(1.4)	29	(2.0)	
Ovulation induction treatment	29	(8.1)	95	(6.6)	
Any	47	(13.1)	142	(9.9)	

Note: The results are presented as *n* (%) or mean (SD). Bold font indicates the statistically significant *p*/RR/CI values.
Abbreviations: IVF, in vitro fertilisation; SD, standard deviation.

3.3 | Perinatal outcomes

Newborn's mean birthweight was lower (3387 ± 680 g) in women with RPL than in the control group (3482 ± 564 g, $p=0.02$). The *prematurity composite* indicated worse outcomes in the RPL group than in control women, but the *neonatal composite* showed similar results (Table 4). Problems related to short gestation and low birthweight (ICD-10: P07) were more commonly diagnosed in the RPL group than in controls (7.2% vs. 3.8%, RR 1.93 [95% CI: 1.22–3.03]). Maternal placental problems diagnosed during the pregnancy or delivery were also seen in the neonatal outcomes, as the risk for the diagnoses of P02 in ICD-10 (newborn affected by complications of placenta, cord, and membranes) was four times higher in the RPL group than in controls (RR 4.00 [95% CI: 1.75–9.15]). The risk of umbilical artery pH <7.10 was higher among the newborns in the RPL group (6.7% vs. 3.6%, $p=0.03$), whereas no differences between groups existed in birth asphyxia diagnoses, Apgar

TABLE 2 Number of previous pregnancies from Medical Birth Register (MBR) in recurrent pregnancy loss (RPL) women and controls.

	RPL women $n=360$		Controls $n=1440$		
	n	(%)	*n*	(%)	*p* Value
Previous pregnancies					**<0.001**
0	32	(8.9)	520	(36.1)	
1	27	(7.5)	436	(30.3)	
2	14	(3.9)	233	(16.2)	
3	83	(23.1)	122	(8.5)	
≥4	204	(56.7)	129	(9.0)	
Previous deliveries (matched primi/multipara)					**0.04**
0	163	(45.3)	652	(45.3)	
1	136	(37.8)	473	(32.8)	
2	34	(9.4)	202	(14.0)	
3	19	(5.3)	56	(3.9)	
≥4	8	(2.2)	57	(4.0)	
Previous caesarean section	38	(10.6)	189	(13.1)	0.19
Miscarriages (self-reported)					**<0.001**
0	66	(18.3)	1164	(80.8)	
1	14	(3.9)	191	(13.3)	
2	31	(8.6)	58	(4.0)	
3	146	(40.6)	21	(1.5)	
≥4	103	(28.6)	6	(0.4)	
Induced abortions					**0.004**
1	41	(11.4)	122	(8.5)	
2	<5		29	(2.0)	
≥3	<5		<5		
Ectopic pregnancies					**<0.001**
1	12	(3.3)	15	(1.0)	
≥2	<5		<5		

Note: Presented as *n* (%). Bold font indicates the statistically significant *p*/RR/CI values.

scores, neonatal intensive care unit admission, or perinatal death. Also, congenital malformations (ICD-10: Q00-Q99) were comparable between the study groups (Tables 4 and S11).

All results remained similar when control women reporting ≥3 previous miscarriages ($n=27$) were excluded from analyses (data not shown).

3.4 | Secondary RPL

We compared all the outcomes between women with secondary RPL ($n=197$) and control women who had previous deliveries ($n=788$) (Tables S2–S6). Most of the same outcomes differed between secondary RPL group and multipara controls than in the primary comparisons except for GDM and PROM, which lost statistical significance. However, SGA was more common in secondary RPL women's newborns than in the multipara women's group (5.1% vs. 2.0%, RR 2.50, [95% CI: 1.15–5.42]). In addition, diagnoses related to slow fetal growth and malnutrition (P05) were more prevalent among secondary RPL women's newborns than in controls (3.6% vs. 0.6%, $p=0.001$).

3.5 | Unexplained and explained RPL

The found risk factors for RPL are presented in Table S1. 15.2% of women with explained RPL ($n=132$) were diagnosed with proteinuria or hypertensive disorders during pregnancy, childbirth, or the puerperium (ICD-10 O10–O16) compared to 5.2% in unexplained RPL group ($n=228$) ($p=0.001$, RR 0.35 [95% CI: 0.18–0.69]) (Table S9), but no difference was found after adjusting for maternal age ($p=0.09$), BMI ($p=0.73$), or both ($p=0.72$). The amount of outpatient visits to maternal care and diagnosed fear of childbirth were similar between the groups. Women with explained RPL used prophylaxis of thromboembolism more often than women with unexplained RPL (14.4% vs. 6.6%, $p=0.02$). Mode of delivery was comparable between the

TABLE 3 Delivery outcomes in recurrent pregnancy loss (RPL) women of their first delivery after RPL examinations and in control women.

	RPL women	Controls			
	n = 360	*n* = 1440	*p* Value	RR	95% CI
Mode of delivery			0.18		
Vaginal	241 (66.9)	960 (66.7)		1.00	0.93–1.09
Vacuum or forceps	30 (8.3)	165 (11.5)		0.73	0.50–1.05
Planned caesarean	31 (8.6)	139 (9.7)		0.89	0.62–1.29
Urgent caesarean	51 (14.2)	155 (10.8)		1.32	0.98–1.77
Emergency caesarean	7 (1.9)	21 (1.5)		1.33	0.57–3.11
Induced labour	101 (28.1)	320 (22.2)	**0.02**	**1.26**	**1.04–1.53**
Placental problems	21 (5.8)	42 (2.9)	**0.007**	**2.00**	**1.20–3.33**
Manual removal of placenta	15 (4.2)	24 (1.7)	**0.004**	**2.50**	**1.33–4.72**
Placenta previa	<5	14 (1.0)	0.81	1.14	0.38–3.45
Placental abruption	<5	<5	0.13	4.00	0.57–28.3
O72 Postpartum haemorrhage	27 (7.5)	76 (5.3)	0.10	1.42	0.93–2.17
Eclampsia	0	<5	0.80	NA	
Shoulder dystocia	0	<5	0.64	NA	

Note: The results are presented as *n* (%) and RR (95% CI). Placental problems include placenta previa, placental abruption, manual removal of placenta and ICD-10 diagnose groups O43 Placental disorders, O44 Placenta previa, O45 Placental abruption. Bold font indicates the statistically significant *p*/RR/CI values.

Abbreviations: CI, confidence interval; RR, risk ratio.

groups, although women with explained RPL delivered by cesarean section slightly more often (28.0% vs. 22.8%, $p > 0.05$). *Neonatal composite* and *placental problems* outcomes were similar between unexplained and explained RPL groups. Neither the birthweight nor the gestational age at delivery differed between the neonates in these comparisons (Tables S7–S10).

4 | DISCUSSION

We show that gestational hypertensive disorders and placental problems are associated with the history of RPL. In perinatal outcomes, preterm birth, lower birthweight, PROM, and placental problems—reflected in the neonatal period—were more common in the RPL group. Women with RPL required more care during their pregnancy, which was seen in the number of outpatient visits and puerperal hospital admission time. The risk profile was similar in pregnancies after secondary RPL compared with multipara controls.

This study confirms the association of RPL with placenta-related disorders affecting pregnancy and perinatal outcomes, as seen in previous studies.[13,14,28] In early pregnancy, a complex network of immunological factors begins to interact locally at the maternal–fetal interface. This interplay continues throughout the pregnancy. The communication between the embryo and endometrium and correct vascular modulation of the placental spiral arteries by the extravillous trophoblast cells are key factors in successful implantation and formation of a well-functioning placenta.[9] The maternal immune system plays a significant role in regulating implantation and placentation. It has been suggested that a continuum of immunological imbalances results in either early miscarriages or preeclampsia, fetal growth retardation, or preterm birth later in pregnancy.[9]

According to the perinatal statistics, the incidence of preterm birth is 5%–6% of all singleton births in Finland,[29] which is in line with our findings of the control group (5.8%), whereas it was more prevalent in the RPL group (8.9%). History of RPL was also associated with PROM. Infection of the reproductive tract is a known cause of PROM. Furthermore, it has been suggested that dysbiosis of vaginal[30] or endometrial[31] microbiome might relate to PROM and preterm birth. However, the exact etiology is still unknown—whether it is a matter of a coincidental, transient pathogen, or a more permanent imbalance of the microbiota in the endometrium. Interestingly, we[32] and others[33,34] have previously shown that dysbiosis of the endometrial microbiome relates to RPL. Microbes may affect the delicate balance of interactions between invading trophoblast and maternal NK cells, as well as other immunological factors regulating placental development, leading to an increased risk of RPL, PROM, and preterm birth. Likely, an infection or dysbiotic microbiota of the reproductive tract is behind some of the preterm births in our study, but we were unable to distinguish the causes of preterm birth or PROM from our register data.

Interestingly, we found that manual removal of the placenta was needed more often in RPL women's deliveries than in the control group. This might be explained by previous uterine procedures in the treatment of pregnancy losses. The association of RPL and placentation problems has not been studied previously.

TABLE 4 Perinatal outcomes of subsequent pregnancy in recurrent pregnancy (RPL) women and controls.

	RPL women		Controls				
Number of singleton newborns	**360**		**1440**				
	n	**(%)**	***n***	**(%)**	***p* Value**	**RR**	**95% CI**
Gestational age (weeks) at delivery					**0.04**		
<37	32	(8.9)	83	(5.8)		**1.54**	**1.04–2.28**
of which <28	5	(1.4)	7	(0.5)		2.86	0.91–8.95
28–36	27	(7.5)	76	(5.3)		1.42	0.93–2.17
≥37	328	(91.1)	1357	(94.2)		1.00	
Sex					0.12		
Male	186	(51.7)	767	(53.3)		0.97	0.87–1.08
Female	173	(48.1)	673	(46.7)			
Neonatal composite (Apgar 5 min 0–6, NICU, perinatal death, Umbilical artery pH < 7.10)	65	(18.1)	213	(14.8)	0.13	1.22	0.95–1.57
Prematurity composite (SGA, gestational age <37, Diagnoses P07, O42, O10-14)	54	(15.0)	147	(10.2)	**0.01**	**1.47**	**1.10–1.96**
Apgar score 1 min					0.31		
0–6	33	(9.2)	103	(7.2)		1.28	0.88–1.86
7–10	325	(90.3)	1333	(92.6)			
Unknown	2		4				
Apgar score 5 min					0.67		
0–6	11	(3.1)	50	(3.5)		0.88	0.46–1.67
7–10	347	(96.4)	1386	(96.3)			
Unknown	2		4				
NICU admission	45	(12.5)	146	(10.1)	0.19	1.23	0.90–1.69
Newborn in the age of 7 days					0.24		
At home	323	(89.7)	1335	(92.7)		0.97	0.93–1.01
At maternal ward	24	(6.7)	78	(5.4)			
At another ward	8	(2.2)	14	(1.0)			
In another hospital	<5		7	(0.5)			
Deceased	<5		6	(0.4)			
Perinatal mortality					0.75		
Perinatal death	<5		6	(0.4)		>1	NS
Umbilical artery pH					**0.03**		
<7.10	24	(6.7)	52	(3.6)		**1.85**	**1.15–2.95**
≥7.10	306	(85.0)	1281	(89.0)			
Unknown	30	(8.3)	107	(7.4)			
Birthweight (g)							
<2500	30	(8.3)	63	(4.4)	**0.002**	**1.90**	**1.25–2.90**
of which <1500	8	(2.2)	15	(1.0)	0.074	2.13	0.91–4.99
1500–2499	22	(6.1)	48	(3.3)	**0.014**	**1.83**	**1.12–3.00**
≥4000	49	(13.6)	213	(14.8)	0.570	0.92	0.69–1.23
Weight in relation to gestational age							
Small for gestational age	17	(4.7)	54	(3.8)	0.40	1.26	0.74–2.15
Large for gestational age	7	(1.9)	34	(2.4)	0.64	0.82	0.37–1.84

TABLE 4 (Continued)

Number of singleton newborns	RPL women 360		Controls 1440				
	n	(%)	*n*	(%)	*p* Value	RR	95% CI
Unknown	17	(4.7)	66	(4.6)			
	Mean	(SD)	Mean	(SD)			
Birthweight (g)	3386.9	(679.8)	3481.7	(564.3)	**0.02**		
Boys	3465.3	(696.0)	3521.4	(564.5)	0.31		
Girls	3320.1	(616.4)	3436.5	(560.8)	**0.02**		
Height (cm)	49.8	(3.4)	50.0	(2.7)	0.35		

Note: The results are presented as *n* (%) and RR (95% CI). Bold font indicates the statistically significant *p*/RR/CI values.
Abbreviations: CI, confidence interval; NICU, Neonatal Intensive Care Unit; RR, risk ratio; SD, standard deviation.

TABLE 5 Maternal diagnoses (ICD-10) during pregnancy and delivery in women with recurrent pregnancy loss (RPL) and controls.

		RPL women *n* = 360		Controls *n* = 1440				
	Diagnosis	*n*	(%)	*n*	(%)	*p* value	RR	95% CI
O10	Pre-existing hypertension complicating pregnancy, childbirth, and the puerperium	<5		7	(0.5)	0.60	<1	NS
O13	Gestational [pregnancy-induced] hypertension without significant proteinuria	**11**	**(3.1)**	**20**	**(1.4)**	**0.03**	**2.20**	**1.06–4.55**
O14	Gestational [pregnancy-induced] hypertension with significant proteinuria	9	(2.5)	33	(2.3)	0.81	1.09	0.53–2.26
O24	Diabetes mellitus in pregnancy	**67**	**(18.6)**	**201**	**(14.0)**	**0.03**	**1.41**	**1.04–1.91**
O24	Adjusted for BMI					0.10	1.33	0.95–1.82
O24.0-O24.1	Pre-existing diabetes mellitus, non-insulin dependent or insulin dependent	5	(1.1)	17	(1.2)	0.75	1.18	0.44–3.17
O24.4	Diabetes mellitus arising in pregnancy	**62**	**(17.2)**	**184**	**(12.8)**	**0.03**	**1.42**	**1.04–1.95**
O24.4	Adjusted for BMI					0.10	1.33	0.95–1.85
O26.6	Liver disorders in pregnancy, childbirth, and the puerperium	5	(1.4)	19	(1.3)	0.92	1.05	0.40–2.80
O32	Maternal care for known or suspected malpresentation of fetus	**12**	**(3.3)**	**22**	**(1.5)**	**0.02**	**2.18**	**1.09–4.37**
O34.3	Maternal care for cervical incompetence	5	(1.4)	<5		**0.01**	**>1**	**SS**
O41.1	Infection of amniotic sac and membranes	5	(1.4)	13	(0.9)	0.41	1.54	0.55–4.29
O42	Premature rupture of membranes	**20**	**(5.6)**	**34**	**(2.4)**	**0.002**	**2.35**	**1.37–4.04**
O48	Prolonged pregnancy	12	(3.3)	53	(3.7)	0.75	0.91	0.49–1.68
O60	Preterm labor and delivery	**17**	**(4.7)**	**38**	**(2.6)**	**0.04**	**1.79**	**1.02–3.13**

Note: The results are presented as *n* (%) and RR (95% CI). Bold font indicates the statistically significant *p*/RR/CI values.
Abbreviations: CI, confidence interval, NS, statistically insignificant, RR, risk ratio; SS, statistically significant.

RPL is a major psychological burden[35,36] these couples carry with them to the following pregnancies. Psychological support and "tender loving care" are recommended in counseling.[20] Couples with RPL hope to have sufficient information, early access to treatment, support, and follow-up sensitive to their history of RPL.[37,38] In our study, RPL women experienced more fear toward the upcoming

delivery than control women, although the difference was statistically non-significant. RPL women had more outpatient visits during pregnancy, and they stayed longer in postpartum care than control women. Whether this was due to somatic or psychological reasons is beyond the scope of this research. Neither do we know whether the amount of support is sufficient for these women. We believe that the stress and worry related to the history of RPL leads to a more active referral policy to the maternity outpatient clinic. This can also be seen as a positive sign of the primary maternal care units' abilities to recognize the risks related to RPL in the following pregnancies.

The major strength of our study is the thoroughly investigated and diagnosed RPL couples' group whose subsequent births and pregnancies were followed using the reliable Finnish MBR register data. MBR has collected information on all newborns in Finland since 1987. Information on midwife records and diagnoses coded by physicians are routinely registered and missing or incorrect information is double-checked from the birth hospitals. The proportion of missing data in MBR is very low. Data quality studies have shown excellent coverage and good validity.[39] Data of the cases and the controls were collected similarly for both groups from the same national register. We were able to compare demographic information, such as lifestyle factors and socio-economic status between groups, which has been lacking in some of the previous large register-based studies.[14,17] Consideration of paternity and that all pregnancies of the RPL couples most likely originate from the same partnership is another strength of our study that has not been accounted for in previous studies.[17,18,40] This study population is based on our previous work about RPL couples' prognosis[23] where we carefully matched that the father of the child was the same spouse than at the time of the RPL investigations. In this study, we used information only from the MBR about women and neonates and therefore were not able to confirm paternity. Based on our previous work, it is very likely that the parents have remained unchanged during the study period.

By selecting matched controls for RPL women from the same register, we were able to control for major confounding factors such as age and parity, as lack of this has been a weakness in some previous birth cohort studies. Our study covers thoroughly the pregnancy, delivery, and perinatal outcomes. As limitations of this study, we might lack power to detect some of the rare obstetric and neonatal outcomes—such as stillbirth and placental abruption—due to the low number of women in the study. Furthermore, due to strict data protection rules, we are not allowed to report outcomes with one to four cases per group.

The subsequent pregnancy's risk profile after secondary RPL was quite similar to the whole RPL population. This is in line with a previous work[14] that found preterm birth, preeclampsia, and placental abruption to associate with both primary and secondary RPL in separate comparisons. Furthermore, their study reported SGA more often in the secondary RPL group compared to multipara controls. In our study, SGA was also observed relatively more often in the secondary RPL group (5.1% vs. 2.0%) than in multipara controls.

We found one or more suspected etiological factors in 37% of our RPL couples; the most common etiological findings in RPL investigations were woman's obesity, hereditary thrombophilia, elevated thyroid peroxidase antibodies, and polycystic ovary syndrome. Previous studies have called for comparisons according to etiology of RPL. Unfortunately, due to the low numbers of RPL women in this study and the rarity of many pregnancy outcomes, this was not possible. However, after etiological and lifestyle examinations, we defined RPL as either explained or unexplained. We found that outcomes were comparable between women with explained and unexplained RPL, which is in line with the overall pregnancy complications of a previous study.[40] In that study, on the contrary, women with unexplained RPL had more preeclampsia and pregnancy-related liver disorders than women with explained RPL, whereas the risk profile in our study was non-significant in favor of the women with unexplained RPL. Our results can be partly reasoned with higher BMI and age in women with explained RPL. These studies differ in defining explained and unexplained RPL, and their proportion of explained RPL in the study population was larger (60%) than ours (37%).

They lost 13.5% of women in follow-up after RPL investigations and 13.7% during pregnancy, whereas we had complete follow-up data on pregnancies and neonates for all RPL women. Generally, we saw only slight, non-significant, differences towards worse outcomes in the explained RPL group. This is reassuring for couples with unexplained RPL and at the same time, encourages professionals to pursue the field of etiological research.

5 | CONCLUSION

The findings of this study accumulate evidence that women with RPL history have elevated risks for some adverse pregnancy outcomes. They should be provided with careful preventive medical attention and tender loving care. However, mostly their pregnancy prognoses were good. Our results inspire future research toward the etiology of RPL, especially the immunological regulation of placenta formation. Growing understanding of early pregnancy could help professionals to reduce the risk of complications in RPL women's future pregnancies.

AUTHOR CONTRIBUTIONS

Hanna Hautamäki (corresponding author) wrote the manuscript, prepared tables and figure, and collected data from the hospital records. Mika Gissler calculated most of the statistical analyses, edited the manuscript, and provided his expertise on the Finnish MBR. Jenni Heikkinen-Eloranta edited the manuscript and provided obstetrical expertise. Aila Tiitinen edited the manuscript and provided funds for research work. Pirkko Peuranpää collected most of the data from hospital records, made statistical analyses, edited the manuscript, and prepared the graphical abstract. All authors designed the study, participated in writing the manuscript, and approved the final version.

FUNDING INFORMATION

This study was funded by Helsinki University Hospital research grants (TYH2020207 and TYH2024329). Hanna Hautamäki has

received grants from The Finnish Cultural Foundation, Juhani Aho Foundation for Medical Research, and the Yrjö Jahnsson Foundation. Pirkko Peuranpää has received grants from the Emil Aaltonen Foundation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Helsinki University Hospital (HUS/138/2017, June 28, 2017) and Findata (THL/4217/14.02.00/2020, October 14, 2020) conferred permissions for this study. In register-based studies, approval from ethics committee is not required in Finland.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: 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*. 2024;00:1-12. doi:10.1111/aogs.15039