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Original Research Article

A cross sectional study of pregnancy outcome in women with recurrent pregnancy loss

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ABSTRACT

Background: Recurrent pregnancy loss occurs in approximately 1-2% of reproductive aged women. Aetiology is unknown in approximately 50% of RPL. Common established causes include uterine anomalies, antiphospholipid syndrome, hormonal and metabolic disorders, and cytogenetic abnormalities. Maternal age and number of previous miscarriages are two independent risk factors. The study was conducted to determine the pregnancy outcomes in women with history of recurrent pregnancy loss.
Methods: A hospital based cross-sectional study was conducted in the Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal. The study was carried out during a period of 2 years with effect from September 2019 to August 2021.
Results: A total of 116 pregnant women with history of recurrent pregnancy loss were included in the study. The mean age among participants was 30.28±5.48 years. The average number of abortions prior to this pregnancy was 2.53±1.02. About 85.34% had spontaneous onset of labour and nearly equal proportion of (48.27% and 46.56%) of the participants delivered by NVD and CS. Maternal complications were present in 51.72%. Most common were hypertensive disorder (12.06%) and preterm labour (12.06%). Fetal complications were observed in 22.4% of newborn, commonest being low birth weight.
Conclusions: Women with history of recurrent pregnancy loss encountered increased adverse maternal complications however fetal complications were similar to that of the general population. The definition, diagnosis and treatment of patients with a history of RPL remains difficult. Increased antenatal surveillance to reduce the risk of pregnancy complications with better screening of the obstetrical history and the necessary investigations to identify a treatable cause associated with previous miscarriages can lead to early prophylactic interventions for a better outcome.

Keywords: Hypertensive disorder, Low birth weight, Preterm birth, Recurrent pregnancy loss

INTRODUCTION

Early pregnancy loss, also referred to as miscarriage or spontaneous abortion, is defined as the loss of a clinical pregnancy before 20 completed weeks of gestational age (18 weeks after fertilization) or, if gestational age is unknown, the loss of an embryo/fetus of <400 g.[1]

Recurrent pregnancy loss is a common clinical problem in reproduction, occurring in approximately 1% of reproductive aged women.[2] Recurrent pregnancy loss (RPL) is defined as the loss of two or more pregnancies as defined by American Society of Reproductive Medicine (ASRM-2013) and the European Society of Human Reproduction and Embryology (ESHRE 2017). The exact prevalence of RPL is difficult to estimate, but most studies report that RPL affects 1-2% of women.[3] RPL may evoke

a psychological trauma to the couple. It has been observed that the risk of future pregnancy losses increases with the number of prior pregnancy losses. A mid-trimester pregnancy loss seems to be associated with a subsequent poor pregnancy prognosis.

For purposes of determining when evaluation and treatment for infertility or recurrent pregnancy loss are appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathologic examination.[4] RPL can be categorised as primary or secondary. Primary RPL refers to multiple losses in a woman with no previous viable infants, whereas secondary RPL refers to multiple losses in a woman who has already had a pregnancy beyond 20 gestational weeks. Tertiary RPL refers to multiple pregnancy losses between normal pregnancies.

The causes of RPL are complex and pathophysiological mechanisms poorly understood. Aetiology is unknown in approximately 50% of RPL and those cases are designated as unexplained RPL.[5] Risk factors for recurrent miscarriage include: loss of a euploid pregnancy, loss after the first trimester, difficulty conceiving, and delivery of a very low birth weight baby.[6]

Common established causes include uterine anomalies, antiphospholipid syndrome, hormonal and metabolic disorders, and cytogenetic abnormalities. Other aetiologies have been proposed but are still considered controversial, such as chronic endometritis, inherited thrombophilias, luteal phase defect, and high sperm deoxyribo-Nucleic Acid (DNA) fragmentation level.[7] Uterine anomaly is found in approximately 10-15% of women with RPL, most common being septate uterus and bicornuate uterus. Maternal genetic mutations (2-5%); endocrine problems such as thyroid disease, are responsible for 15-20% of miscarriages.

Other endocrinology disorders may include polycystic ovary syndrome, insulin resistance, uncontrolled diabetes mellitus, hyperandrogenemia. Other causes include autoimmune diseases, alloimmune abnormalities, infections. Inherited thrombophilias causes intravascular and placental intervillous thrombosis. These include factor V Leiden mutation, prothrombin G20210A gene mutation, protein S deficiency, protein C deficiency, antithrombin deficiency, and methylenetetrahydrofolate reductase (MTHFR) mutations in the pathogenesis of RPL. Anti-phospholipid antibodies (APAs) occur in one fifth of patients with RPL. Alloimmune miscarriages refer to the impairment of the maternal alloimmune response to paternally generated molecules on trophoblasts leading to unacceptability of the semi-allogeneic fetus.

Maternal age and number of previous miscarriages are two independent risk factors for a further miscarriage. A large prospective register linkage study reported the age-related risk of miscarriage in recognised pregnancies to be: 12-19 years, 13%; 20-24 years, 11%; 25-29 years, 12%; 30-34 years, 15%; 35-39 years, 25%; 40-44 years, 51%; and ≥45 years, 93%. Advanced paternal age has also been identified as a risk factor for miscarriage. The risk of miscarriage is highest among couples where the woman is ≥35 years of age and the man ≥40 years of age.[8]

In approximately 2-5% of couples with recurrent pregnancy loss, one of the partners carries a balanced structural chromosomal anomaly, most commonly a balanced reciprocal or Robertsonian translocation.[8] Some studies have shown an increased prevalence of chronic endometritis in women with RPL (10-27%).[9]

Various treatment modalities involve administration of low dose aspirin plus heparin in patients with antiphospholipid syndrome (APS), genetic counselling, pre-implantation genetic diagnosis, cervical cerclage, heparin therapy in women with second trimester abortion with inherited thrombophilias. Ensuring adequate control of thyroid disorders and diabetes mellitus. Women with unexplained RPL have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of an early pregnancy assessment unit.[8] The prognosis of RPL is encouraging even with the diagnosis of RPL and as many as 4 to 5 prior losses, a patient is more likely to carry her next pregnancy to term than to have another loss.[10]

The study was conducted to determine the pregnancy outcomes in women with history of recurrent pregnancy loss.

METHODS

A hospital based cross-sectional study was conducted in the Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal. The study was carried out during a period of 2 years with effect from September 2019 to August 2021. Ethical Approval was obtained from the Institute Research Ethics Board, Regional Institute of Medical Sciences, Imphal before commencement of the study. Signed Informed Consent was taken from all the participants. Details of all the participating individuals was kept confidential.

Inclusion criteria

Pregnant patients with history of two or more than two pregnancy losses with or without a previous live birth were included.

Exclusion criteria

Multiple pregnancies and those who were not willing to participate were excluded from study.

Independent variable: Age, educational qualification, occupation, blood pressure, weight, height, Body-mass Index, personal history (dietary habits, smoking, alcohol consumption, tobacco) parity, gravidity, antenatal history

(seropositive), history of recurrent pregnancy losses, period of gestation, onset of labour, progress of labour, mode of delivery, menstrual history.

Dependent variable: pregnancy outcome includes any maternal complications like post-partum haemorrhage (PPH), Gestational Hypertension (GHTN), anemia and fetal outcome like live birth, still birth, intrauterine death (IUD), term, preterm, low birth weight, big baby, neonatal sepsis, any congenital anomalies.

Study procedure

Data was collected after taking informed consent before starting the study. Data was collected in predesigned structured proforma. Detailed history including age, menstrual history, parity, history of previous pregnancies, recurrent abortions (spontaneous or induced), preterm delivery etc, family history, gestational age and suitable risk factors like socioeconomic status, education, occupation etc. The patient were followed up and all the details of pregnancy outcome like preterm delivery, Premature rupture of membrane (PROM), PPH, obstructed labour, vaginal delivery or caesarean section, malpresentation, intrauterine growth restriction (IUGR) etc. was taken from the delivery register / records.

Statistical analysis

The data entry and analysis were done using SPSS version 21. Descriptive statistics like frequency, mean, percentage, standard deviation was used. Unpaired t test and Chi square test was used to see the association between the pregnancy outcome and some variables of interest. A P value <0.05 was taken as significant.

RESULTS

In the present cross sectional observational study, 116 pregnant women with history of recurrent pregnancy loss, fulfilling the inclusion criteria were taken up.

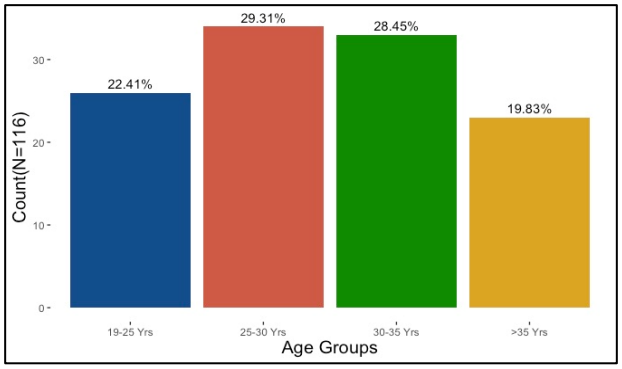

Figure 1: Age distribution among the study participants (N=116).

The mean age of the study participants was 30.28±5.48 years. Majority of them were of 25-30 years of age (29.34%) followed by 30-35 years (28.45%). Among them 19.83% were of more than 35 years of age. The minimum age recorded was 19yrs and maximum was 42 years of age (Figure 1).

Among the study participants, only 2.59% were illiterate. Majority of them (45.69%) were studies up to high school level followed by intermediate level (33.62%). 18.10% had completed their graduation (Figure 2).

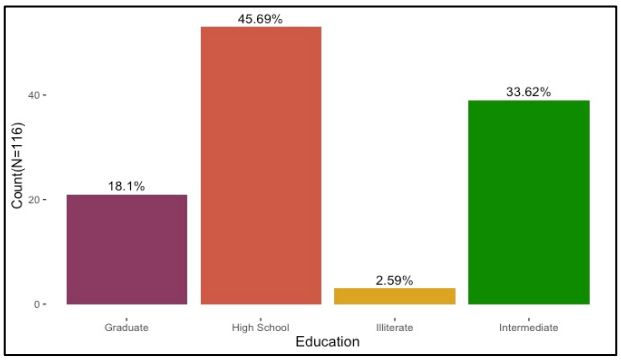

Figure 2: Level of education among the study participants.

Table 1: Abortion history and previous obstetric history of the study participants (N=116).

No. of abortion	N (%)
Mean±SD	2.53±1.02
≤3	104 (89.66)
>3	12 (10.34)
Parity	
P0 (Nulliparous)	25 (21.55)
P1 (Primi-parous)	91 (78.45)

Table 2: General history of the study participants (N=116).

Parameters	N (%)
Personal history	
No addiction	114 (98.28)
Drug abuse	1 (0.86)
Tobacco	1 (0.86)
Medical/surgical history	
Normal	98 (84.48)
Uni-cornuate uterus	1 (0.86)
Bicornuate uterus	1 (0.86)
Large sub-serosal fibroid	1 (0.86)
Chronic hypertension	1 (0.86)
Seizure disorder	1 (0.86)
Covid positive	2 (1.72)
Drug abuse	1 (0.86)
Primary infertility	1 (0.86)
Systemic lupus erythematosus (SLE)	1 (0.86)
Subclinical hypothyroidism	8 (6.90)

Table 3: Descriptive statistics of maternal outcome among the study participants (N=116).

Parameters	N (%)
Mode of onset of labour	
Induced	17 (14.66)
Spontaneous	99 (85.34)
Mode of delivery	
Normal vaginal delivery (NVD)	56 (48.27)
Cesarean section (CS)	54 (46.56)
Assisted breech vaginal delivery	1 (0.86)
Breech vaginal expulsion of dead fetus	1 (0.86)
Preterm vaginal delivery	3 (2.59)
Vaginal expulsion of dead fetus	1 (0.86)
Instrumental	
Yes	2 (1.72)
No	114 (96.61)

Table 4: Maternal complication among the study participants (N=116).

Maternal complications	N (%)
Complications	
Yes	60 (51.72)
No	56 (48.28)
Types of complications	
Chronic HTN	1 (0.86)
GHTN	12 (10.34)
Severe preeclampsia	1 (0.86)
Oligohydraminous	6 (5.17)
Severe oligohydraminous	3 (2.58)
Polyhydraminous	1 (0.86)
Anemia	3 (2.58)
Abruptio placentae	1 (0.86)
Low lying placenta	2 (1.72)
BREECH	7 (6.03)
Cervical incompetence	1 (0.86)
Gestational diabetes mellitus (GDM)	2 (1.72)
IUGR	6 (5.17)
Non-progression of labour	1 (0.86)
Previous CS	21 (18.10)
POST TERM	1 (0.86)
PRETERM	14 (12.06)
PROM	8 (6.89)
PRETERM PROM	1 (0.86)
RH negative	2 (1.72)
Transverse LIE	2 (1.72)
PPH	3 (2.58)

The average number of abortions prior to this pregnancy among the study participants was 2.53±1.02. Majority of them (89.66%) had 2-3 prior abortion and only 10.34% had more than 3 abortion history. Among the study participants, 91 (78.45%) were primi-parous and rest 21.55% were nulliparous (Table 1).

Among the participants, 114 (98.28%) did not have any addiction. Only 2 people had history of addiction which included one each for drug and tobacco addiction. Out of 116 participants, 98 (84.48%) had no previous surgical or medical complications. Among those having medical/surgical conditions (15.51%), the details about their conditions were mentions in Table 2.

Table 5: Descriptive statistics of the foetal outcome among the study participants (N=116).

Parameters	N (%)
Intra-uterine age	
Term	101 (87.07)
Preterm	14 (12.07)
Post-Term	1 (0.86)
Outcome status	
Live	114 (98.27)
IUD	2 (1.72)
Sex	
Female	61 (52.59)
Male	55 (47.41)
Weight (Kg)	
Mean (SD)	2.95 (0.59)

Table 6: Foetal complications among the study participants (N=116).

Parameters	N (%)
Requirement of resuscitation	
No	104 (89.65)
Yes	10 (8.70)
Admission to NICU	
No	103 (88.79)
Yes	11 (9.48)
Complications	
Yes	26 (22.41)
No	88 (75.86)
Types of complications	
Extremely LBW	2 (1.60)
Very LBW	3 (2.40)
LBW	11 (9.48)
Very large baby/ macrosomia	1 (0.80)
Birth asphyxia	2 (1.60)
IUGR	5 (4.00)
Meconium aspiration	1 (0.80)
Neonatal sepsis	1 (0.80)
No	88 (75.86)

About 99 (85.34%) had spontaneous onset of labour and rest, 17 (14.66%) were induced. Nearly equal proportion of (48.27% and 46.56%) of the participants delivered baby by NVD and CS (Table 3).

Among the study participants, 60 (51.72%) had shown various complications whereas 56 (48.28%) did not show any complication due course of their current pregnancy.

The proportions of various complications shown among them was illustrated in Table 4.

Out of 116 babies delivered, 101 (87.07%) were term, 14 (12.07%) were pre-term and only one was post-term baby. Among them, 114 (98.27%) were live foetus and two died in-utero (Table 5).

Out of 116 babies born, 104 (89.65%) did not require resuscitation, however, 10 (8.70%) resuscitated. Among the babies born, 11 (9.48%) admitted to NICU. Regarding post birth complications, 88 (75.86%) did not have any complications, however, 26 (22.41%) had several complications. The list of complications among the child born was listed in Table 6.

Table 7 shows correlation between socio-demographic profile and previous obstetrics history with maternal complications in which were not significant statistically.

Table 7: Correlation between socio-demographic profile and obstetric history with maternal complications.

	Complication (N=60)	No complication (N=56)	Total (N=116)	P value
Age				0.89*
Mean (SD)	30.22 (5.93)	30.36 (5.00)	30.28 (5.48)	
Range	19.00 - 42.00	20.00 - 40.00	19.00 - 42.00	
Education class (%)				0.82#
Graduate	10 (16.7)	11 (19.6)	21 (18.1%)	
High school	26 (43.3)	27 (48.2)	53 (45.7%)	
Illiterate	2 (3.3)	1 (1.8)	3 (2.6%)	
Intermediate	22 (36.7)	17 (30.4)	39 (33.6%)	
No of abortions (%)				0.48
Mean (SD)	2.60 (1.21)	2.46 (0.76)	2.53 (1.02)	
Range	2.00 - 9.00	2.00 - 5.00	2.00 - 9.00	
No abortion class (%)				0.63
2 to 3	53 (88.3)	51 (91.1)	104 (89.7%)	
More than 3	7 (11.7)	5 (8.9)	12 (10.3%)	

*Unpaired t test; #Chi-square test

DISCUSSION

For a women, pregnancy and childbirth brings joy in her life. RPL has been public health concern with an incidence of 1 to 2%. It causes psychological impact in the form of emotional stress, anxiety, grief, depression in the mother and the family.

In this present study, the mean age of participants was 30.28 ±5.48. Majority of them were of 25-30 years of age (29.34%) followed by 30-35 years (28.45%). The minimum age recorded was 19years and maximum was 42 years of age. This is comparable to the studies conducted by Miyaji et al (34years) and Egerup et al (<33years) and Kotani et al (34.3years) and Youseff et al (33.7years).[11-14] About 23 (19.83%) of the participants were above 35 years of age. This could be due to late marriage among the participants. With the increased number of pregnancy losses, the age of the woman increases. (Lund et al, 2010; Kolte et al, 2014).[15,16]

In our study the highest number of the participants (45.69%) had education till high school whereas only 18.10% studied till graduation and 2.59% had no formal education. Most of the patients are less aware of recurrent pregnancy losses and hence no treatment seeking attitude.

The average number of abortions prior to this pregnancy among the study participants was 2.53±1.02. Majority of them (89.66%) had 2-3 prior abortion and only 10.34% had more than 3 abortion history. This is comparable to a study conducted by Gabbai et al where the mean no of previous abortions was 3.19, a mean of 3 in the study by Kling et al, a mean of 2.5 by Kotani et al and a mean of 2.89 by Ticconi et al.[17,18,13,19] Various studies have found that the risk of future pregnancy loss increases with the number of prior pregnancy loss. (Clifford et al, 1997; Kolte et al, 2014).[10,16]

Out of 116 participants, 98 (84.48%) had no surgical or medical complications. Among those having medical/surgical conditions (15.51%), sub clinical hypothyroidism was found to be the most common endocrinological factor associated in about 6.9% of the participants. Other conditions included 2 cases each of uterine anomalies and Covid 19 infection. And 1 each for chronic hypertension, large sub-serosal fibroid, SLE, primary infertility, drug abuse, seizure disorder. Many might have had an underlying cause that was not evaluated.

Among the participants, 114 (98.28%) did not have any addiction. Only 2 people were found to have some kind of addiction. One of them was a drug addict and another was tobacco addict. Two of the studies found that cigarette smoking significantly increased the risk of RPL within the

general population.[20,21] Other studies have shown that the effects of smoking in elevating the risk of RPL were nonsignificant, although the effects increased with the amount of cigarettes smoked per day and this trend was significant.[22] Alcohol intake compared with no alcohol intake increases the risk of RPL, however this is not statistically significant (All three studies demonstrated that alcohol does not have a statistically significant effect on the risk of RPL within the general population.[20,21,23] Caffeine has been shown to increase the risk of RPL in a dose-dependent manner, with consumption of >300 mg caffeine/day being associated with the highest risk.[20,21] Other studies have shown that caffeine consumption has no effect on the risk of RPL within the general population.[23] Several studies have suggested that factors such as obesity, smoking, alcohol, caffeine and exposure to certain occupational hazards may increase the chance of RM (Saravelos and Regan, 2011), and this could predominantly concern the unexplained RM group.[24]

Among the study participants, 60 (51.72%) had shown various complications whereas 56 (48.28%) did not show any complication due course of their current pregnancy. Most common complication observed was hypertensive disorder of pregnancy (1 chronic hypertension, 12 GHTN, 1 severe preeclampsia) and Preterm labour 14(12.06%), 7.75% oligohydraminous (6- mild and 3-severe), 6.89% of PROM, 6.03% Breech presentation, 5.17% IUGR. Many of the patients had more than one complication. This study was comparable to Ticconi et al, where 10.7% had preeclampsia and GDM each, 6.49% had preterm PROM, 3% oligohydraminous, 1% polyhydraminous, 3.2% IUGR and 2.5% placenta previa and 5.6 % abruptio placentae.[19] Gabbai et al showed that about 22.9 % had preterm birth.[17] Similarly, a study conducted by Roepke et al showed 4.3% of preeclampsia, 10% of preterm birth,1% placental abruption.[25] A study conducted by Kling et al showed similar results with 4% having preeclapmsia, 5.7% having GDM, 3.4% premature labour, 2.3% PROM, 0.6% placenta previa, 1.1% placental abruption, 4.6% of cervical incompetence.[26] A large-scale birth cohort study conducted by Ogasawara et al in Japan showed similar results.[27]

Out of 116 babies delivered, 101 (87.07%) were term, 14 (12.07%) were pre-term and only one was post-term baby. Among them, 114 (98.27%) were live foetus and two died in-utero. The mean birth weight observed was 2.95 kg. 13.7% babies had birth weight below 2.5 kg while one (0.84%) had birth weight above 4 kg.

Out of 116 babies born, 104 (89.65%) did not require resuscitation, however, 10 (8.70%) resuscitated. Among the babies born, 11 (9.48%) admitted to NICU and most common indication being low birth weight. Regarding post birth complications, 88 (75.86%) did not have any complications, however, 26 (22.41%) had several complications like 11 (9.48%) low birth weight, 2 (1.60%) extremely LBW, 3 (2.40%) very LBW, 2 (1.60%) birth asphyxia, 1 (0.80%) each for meconium aspiration and neonatal sepsis. A historical study with 732 719 nulliparous women conducted by Williams et al, who had a first live birth showed that women with RM were at the greatest risk (adjusted OR 1.73; 95%CI 1.57-1.90) and the greatest association was with extreme PTB (24-28 weeks).[28] In a study conducted by Roepke et al observed that, the risk of preterm stillbirth, but not of stillbirth at term, was significantly higher in women with RPL compared to references.[25] The rates of a preterm stillbirth were 0.5% vs. 0.2% in RPL women vs. reference women in their study.[27]

In the present study there was no significant association between age and education class with the maternal complications among the study participants ($p>0.05$). Similarly there was no association found between total number of previous history of abortions with maternal complications.

One of the major limitations of our study is the small sample size owing to the time constraint and hence the results could only be generalizable to the similar setting. The cross-sectional nature of the study confers that the cause-effect relationship cannot be ascertained through our study. However our study is novel of the kind and hence it could serve as a base for further studies to come.

CONCLUSION

It is inferred from our study that women with history of recurrent pregnancy loss encountered increased adverse maternal complications however fetal complications were similar to that of the general population. The definition, diagnosis and treatment of patients with a history of RPL remains difficult. The majority of sporadic early pregnancy losses before the 10 weeks are due to chromosomal errors. Endocrine disorders play an important role in RPL, especially in the early stages of gestation. Women with RPL should be considered as high-risk and undergo increased antenatal surveillance to reduce the risk of pregnancy complications. Identifying the risk factors and their modification, better screening of the obstetrical history and the necessary investigations to identify a treatable cause associated with previous miscarriages and can lead to early prophylactic interventions for a better outcome. Evidences from already conducted trials shows promising results with many therapies likes IVIG, paternal lymphocyte therapy and combination corticosteroids + low dose acetylsalicylic acid + unfractioned heparin, GM-CSF, low dose aspirin + low molecular weight heparin. However there is no universal treatment for women suffering from RPL and combination of therapies should be used for individual patients.

Lastly as the women with RPL suffer from anxiety and emotionally deprived, any kind of supportive behaviour from their partners and family members will improve the mental state of the patient.

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