Original article:

“An observational study of maternal and perinatal outcome in patients of recurrent pregnancy loss in rural population”

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Abstract

Introduction: Our aim was to assess the maternal and perinatal outcome following management and outline basic evaluation of patients with Recurrent Pregnancy Loss.

Methodology: A longitudinal observation study was carried out in the Obst and Gynae department, Pravara Hospital. The study enrolled 70 patients aged 18 to 44 years with history of at least two or more miscarriages less than 20 weeks gestation. They were divided into 3 groups - Group A patients with history of two or more pregnancy losses who reported to OPD immediately after abortion of their last pregnancy; Group B - patients with history of recurrent pregnancy loss but < 20 weeks of gestation in their present pregnancy at the time of inclusion in study; Group C - patients with history of recurrent pregnancy loss but more than 20 weeks gestation in their present pregnancy at the time of inclusion in the study. These patients were followed up in the subsequent pregnancy and maternal and perinatal outcomes were observed.

Results: Advancing maternal age as well as previous unsuccessful pregnancies directly influence the outcome of next pregnancy. One or more previous live birth have a positive influence on next pregnancy with 87.5% success rate, while previous pregnancies ending in abortions and a bad obstetric history had 74% and 66.6% success rates respectively. Overall successful outcome in subsequent pregnancy after intervention was 77.1% of which 71.5% were term deliveries. Obstetric complications observed among the study group included gestational hypertension, abruption, severe oligohydramnios, IUGR, and prematurity. 20.4% neonates required NICU admission.

Conclusion: From our study we conclude that the knowledge of factors such as maternal age at conception, reproductive history, and number of miscarriages in a RPL patient is essential for the assessment of risk of abortion in next pregnancy. RPL patients should be carefully monitored in first trimester of next pregnancy as this is observed to be the most perilous time in such patients. Although the cause remained unexplained in 65% cases, a good outcome was observed even with supportive care.

Introduction: According to Novak’s (1), Recurrent abortion is defined as three or more clinically recognized pregnancy losses before 20 weeks from the last menstrual period. Using this definition, recurrent pregnancy loss occurs in approximately 1 in 300 pregnancies. RCOG Guidelines (2) also define
Recurrent miscarriage as the loss of three or more consecutive pregnancies, and affects 1% of couples trying to conceive. However, some authors like Quenby and Farquharson 1993 (3) ; Stephenson et al 1998 included two or more miscarriages in their studies(4). The Practice Committee of the American Society for Reproductive Medicine (5)(2008)defines recurrent pregnancy loss as two or more failed pregnancies. AJ Drakeley et al (6) and Stirrat et al (7), studied RPL patients with two or more pregnancy loss as the risk of subsequent abortions is high even with two abortions .Niekerk van E C et al 2013, (8) defined RPL as more than 2to 3 consecutive miscarriages occurring before 24 weeks gestation. Some studies suggested that the modern social habit is to conceive at an older age; thus possible investigation and treatment might be initiated too late, therefore they recommend investigations following two or more abortions. In the present study, patients with two or more consecutive abortions, at less than 20 wks of gestation, including both primary as well as secondary miscarriages, have been studied.

Recurrent Pregnancy Loss , even though it is an uncommon condition , but it is an enigma as the underlying cause mostly eludes the clinician , making diagnosis and treatment extremely difficult. Therefore, RPL is a highly important clinical entity for study , research and analysis . Despite numerous studies evaluating causes, investigations , management , and outcome , nothing can be carved into stone yet , as the results of the studies are conflicting or controversial . This further increases the need for more research into this condition. Also, a number of studies have evaluated causes of RPL but, not much has been studied about its outcome in next pregnancy . A lot more studies are required on this entity , and the present study is one such attempt in this direction.

**Materials n methods:**

Duration and place of study:Study was carried out for a period of two year from-1st Sept. 2012 to 31st Aug. 2014 in the Department of Obstetrics and Gynecology, Rural Medical College,Loni.

Study design :Observational Study

Study population: All patients seen in OPD/IPD of Obstetrical and Gynecological Dept. meeting the inclusion criteria

Sample size: Approximately 70 cases

Inclusion criteria :Women ages 18 to 44 years of age with history of at least two or more miscarriages less than 20 weeks gestation.

Data collection-

Sources: Indoor/outdoor case records and Hospital medical record department.

Data storage :On serially numbered structured proforma and master chart.

**Methodology**

All patients with history of two or more pregnancy loss evaluated in OPD/IPD in Pravara Hospital and meeting inclusion criteria were studied.

A detailed clinical history ,thorough clinical examination and investigations with a certain group of pre-decided laboratory tests and special tests wherever relevant and possible, were done through a pre-structured proforma.

Wherever a cause for RPL was determined, treatment was given as per standard protocols and patient was followed up in all cases to determine maternal and foetal outcome.

In these patients, the fetomaternal outcome was studied along the following lines-

1. OBSTETRIC COMPLICATIONS- like hypertensive disorders in pregnancy,
abruption, IUGR, prematurity, oligohyramnios, IUFD or any other illness

2. MODE OF DELIVERY – Normal vaginal delivery or caesarean section.

3. NEONATAL OUTCOME- preterm, term, IUGR, requiring NICU admission.

Observations and results

1) Obstetric status at the time of inclusion in study
At the time of inclusion in study, patients were divided into three groups - 34% patients had a history of 2 or more pregnancy losses and came with a recent abortion. Whereas 66% patients had history of 2 or more prior abortions, but were pregnant at the time of inclusion, of which, 19% were <20wks gestation and 47% were >20 wks gestation.

2) Causes of RPL Found After Investigation and Evaluation
Among the various causes of RPL found in the undertaken study, Anatomical causes were found 20% of patients, endocrine and infective causes were seen in 6% each and autoimmune causes were seen in 3% patients. However in about 65% patients no definite cause was found and etiology was attributed as idiopathic.

3) Treatment given to RPL patients based on underlying cause:
Of the 70 Recurrent Pregnancy Loss patients included in the study, 24.3% patients were managed surgically (eg. Cervical cerclage, hysteroscopic Metroplasty), 14.3% patients were given treatment specific to their underlying medical cause, while 61.4% patients were given supportive care (folic acid, low dose aspirin, antioxidants, nutritional supplements, assurance, regular follow up) depending on the underlying cause.

4a) Pregnancy outcome in patients in group A enrolled in post abortion status in the study:
Majority of patients, i.e. 18 (75%) had sustained pregnancy whereas 1 patient (4.2%) did not conceive and 5 patients i.e. 20.8% aborted.

4 b) Sustained pregnancy outcome in post-abortion group patients: group A
Amongst the 18 patients who conceived and had sustained pregnancy (beyond >20 wks) 8 patients (45%) delivered beyond 37 weeks of gestation i.e. full term newborns, 5 patients (27.7%) delivered before 37 weeks of gestation i.e. preterm newborns, with one patient having IUD, while 5 patients (27.7%) of patients are still under follow up.

5). Pregnancy outcome in patients with less than 20 weeks gestation at time of enrollment: group B
All the 13 patients in this group continued pregnancy beyond 20 weeks. Patients who sustained pregnancy beyond 20wks, were followed up. Out of these 13 patients, 9 patients delivered at term, 3 patients had preterm deliveries, while 1 ANC is under follow up with 5 month gestation. Majority of patients i.e. 69% continued pregnancy beyond 37 weeks of gestation, 23% of patients had pregnancy before 37 weeks and 8% are still under ANC follow-up.

6) Pregnancy outcome in patients with more than 20 weeks gestation at time of enrollment: group C
Outcome of patients enrolled with gestation more than 20 weeks after investigation and management is shown above. Two patients had intrauterine fetal death, seven patients (i.e. 21%) delivered at less than 37 weeks gestation with 4 delivered by NVD and 3 by LSCS. Majority of patients i.e. 70% delivered beyond 37 weeks gestation

7) Relation of number of previous consecutive abortions with present pregnancy outcome
Patients with history of 2 consecutive abortions -3 patients (8%) aborted again while 91.1% were successful in the present pregnancy. In patients with history of 3 consecutive abortions – 88% had successful outcomes while 1 patient did not conceive and one patient aborted again. In patients with history of 4 consecutive abortions, successful outcomes were observed in 66.7% while 33% aborted. In patients with equal to 5 and more abortions, no successful outcome was observed. Also, 6 patients were under follow up with present pregnancy more than 20 wks gestation.

8) Pregnancy outcome in patients with primary Recurrent pregnancy loss and secondary RPL

Patients with no successful pregnancy in the past i.e. primary RPL showed 81.1% successful outcome in the present study whereas unsuccessful outcome was seen in 14.6% patients. Whereas, patients who had even one successful pregnancy in the past, showed 87.5% successful outcome in the present study, with unsuccessful outcome in 12.5%.

9) Influence of previous obstetric history on present pregnancy outcome

Among patients who had had only recurrent miscarriages in the past, successful outcome was observed in 36 women (75%), while, those who had even a single successful pregnancy in the past followed by consecutive abortions, showed 85.5% success rates. Patients with more than one successful pregnancy in the past followed by consecutive abortions showed the most positive outcome in their present pregnancy. In Patients with bad obstetric history, 66.6% showed a positive outcome in the present pregnancy, however, IUGR, low birth weight and prematurity was observed to be higher in this group.

10) Ante partum complications observed in patients with history of RM in present pregnancy

Obstetric complications in the patients of RPL, in present study, were observed. Overall incidence of hypertensive disorders in pregnancy was 11.4%, of which 5.7% were preeclampsia. Abruptio 4.2%, IUGR in 12.8%, multifetal pregnancy in 7%, severe oligohydramnios in 8.7%, preterm in 18.5%, IUFD in 1.7%, while no obstetric complications were seen in 71.4% patients.
Ante partum complications observed in patients with history of RM in present pregnancy

<table>
<thead>
<tr>
<th>Antepartum complications</th>
<th>No. of cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy induced hypertension</td>
<td>4</td>
<td>5.7%</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>4</td>
<td>5.7%</td>
</tr>
<tr>
<td>Abruption</td>
<td>3</td>
<td>4.2%</td>
</tr>
<tr>
<td>IUGR</td>
<td>9</td>
<td>12.8%</td>
</tr>
<tr>
<td>Multifetal pregnancy</td>
<td>4</td>
<td>7%</td>
</tr>
<tr>
<td>Severe oligohydramnios</td>
<td>5</td>
<td>8.7%</td>
</tr>
<tr>
<td>Pre term</td>
<td>13</td>
<td>18.5%</td>
</tr>
<tr>
<td>IUFD</td>
<td>1</td>
<td>1.7%</td>
</tr>
<tr>
<td>No complications</td>
<td>50</td>
<td>71.4%</td>
</tr>
</tbody>
</table>

11) **Overall perinatal outcome following management:**

Overall perinatal outcome following management in all groups is shown here. One patient had IUD, in two patients, baby died due to prematurity and very low birth weight. Overall, 5.3% patients had poor outcome. 22.8% patients had preterm delivery and majority of patients about 71.9% had term delivery.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine Death + Neonatal Demise</td>
<td>3</td>
<td>5.3%</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>13</td>
<td>22.8%</td>
</tr>
<tr>
<td>Term Delivery</td>
<td>41</td>
<td>71.9%</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>100%</td>
</tr>
</tbody>
</table>
12) Neonatal Outcome Based On Level Of Care Required:
Nearly 40% of Preterm Neonates required NICU admission due to various causes whereas other 60% needed only routine neonatal care. Amongst Term Neonates only 12.2% required NICU admission and 90% were shifted to mother side and given routine neonatal care.

13) RPL Patients Who Conceived And Are Under Antenatal Follow Up:
Some of RPL patients who were included in the study and managed as per underlying cause are still under follow up so there pregnancy outcome is awaited. 2 patients are under follow-up with less than 20 weeks gestation and 4 patients are under follow-up with more than 20 weeks gestation pregnancy.

Discussion:
Recurrent pregnancy loss has been a Rubik’s puzzle in the field of obstetrics and gynecology since long. Extensive and varied studies in the past as well as recent times have been successful in identifying certain factors which may be associated with RPL, but none of these studies has compared the prevalence of these factors in normal population. Moreover, a universal definition of recurrent pregnancy loss has not been used. Therefore, the incidence, causes, outcomes among various studies is variable, conflicting or controversial. The present study was aimed at assessing the maternal and perinatal outcome in rural population. Total 70 patients with history of two or more consecutive pregnancy loss, in the reproductive age group, were included and studied. Successful pregnancy outcome in some studies was considered if the study pregnancy progressed beyond 24wks gestation, however, in the present study, pregnancy outcome was considered successful if the study pregnancy ended in a live birth. In these patients, the fetomaternal outcome was studied along the following lines-

OBSTETRIC COMPLICATIONS- like hypertensive disorders in pregnancy, abruption, IUGR, prematurity, oligohyramnios, IUFD or any other illness

MODE OF DELIVERY – Normal vaginal delivery or caesarean section.

NEONATAL OUTCOME- preterm, term, IUGR, requiring NICU admission.

Among the various causes of RPL found in the undertaken study, anatomical causes were found 20% of patients. These included cervical insufficiency in 15 patients and uterine malformations in 4 patients, of which septate uterus was present in 2 patients (~50%), bicornuate uterus in one (~25%) and arcuate uterus in one patient (~25%).

Saito et al(9) and Jivraj et al (10) reported the rate of anatomical causes as 9% and 7% respectively. Grimbizis GF et al (2001), (11) found the mean incidence of septate uterus ~35%, bicornuate uterus ~25% and arcuate uterus ~20%.

Endocrinal etiology was diagnosed in 6% patients, of which, 2 patients had gestational diabetes mellitus and two were diagnosed with hypothyroidism. This was consistent with Saito et al who reported the rate of endocrinal causes in 6.9% cases of which 2.9% had hypothyroidism, 1.2% had diabetes and 2.8% had hyperthyroidism. In the study by Jivraj et al(10) endocrine pathology was found in 13.5% cases. Infective causes were seen in 6%. Autoimmune causes were seen in two patients i.e. 3% patients. This included systemic lupus erythematos and antiphospholipid syndrome. Due to high cost of karyotyping, genetic causes could not be evaluated in our study. In about 65% patients no definite cause
was found, also because some of them were pregnant at the time of inclusion in study and etiology was attributed as unexplained. This was consistent with study by Jivraj et al (10) wherein rate of unexplained RPL was 66%, while Saito et al (9) found that 30% cases were unexplained. 24.3% patients were given specific surgical treatment. In 15 patients MacDonald Cervical cerclage was done. All 15 patients had successful pregnancies beyond 28 wks gestation, however, two patients had preterm deliveries at 36 wks gestation. Success rate with cervical encirclage being 86.7%. D'Addato et al reported a successful pregnancy outcome of 73.3% after cervical cerclage. Hysteroscopic Metroplasty for septate uterus was done in one patient. The patient conceived again, but aborted at 8 wks gestation, signifying an overlapping cause or multiple causes leading to recurrent losses. Second patient with septate uterus was included in study at more than 20 wks gestation. Patient was 32 weeks gestation without surgical correction of the septum. This again indicates that one factor may not be solely responsible for recurrent losses. Two or more overlapping factors or different factors may be present in the same or different pregnancies. Bicornuate uterus was detected in one patient who eventually had a successful outcome. These patients with surgical causes were given specific treatment as mentioned earlier along with supportive therapy, dietary advice, reassurance, and frequent follow up. In the present pregnancy, 10 patients (14.3%) were diagnosed with medical causes, which may be responsible for abortions. These patients were given treatment specific to their underlying medical cause along with supportive care. Four patients’ high vaginal swab showed presence of bacterial vaginosis and Chlamydia trachomatis. They were given doxycycline 100mg BD for 5 days and metronidazole 400mg for 5 days, before conception. Two patients were diagnosed with gestational diabetes mellitus and were given insulin. 2 patients had hypothyroidism with TSH levels at 8 mIU/L and 11 mIU/L respectively. They were treated with thyroxine 100 microgram OD. Autoimmune factors responsible for RPL were diagnosed in two patients, which were-Systemic lupus erythematosis and antiphospholipid syndrome. Patient with SLE, reaborted in present study while, patient with APLA is on heparin and is under follow up at present. 43 patients (61.4%) were given supportive care (folic acid, progesterone, low dose aspirin, antioxidants, nutritional supplements, reassurance, and regular follow up).

Subsequent Pregnancy Outcome according to the number of previous Miscarriages in Patients with Recurrent Pregnancy Loss

The present study showed that as the number of abortions increased, successful outcome in the subsequent pregnancy decreased. Patients with history of two abortions had 91.1% successful outcome in the present pregnancy as compared to patients with history of four abortions whose successful outcome in present pregnancy decreased to 66.7%. In the present study, one patient had history of 5 abortions and one patient had history of 10 abortions. Both patients had poor outcome in present pregnancy. However, due to the lesser number of subjects, this requires further study. The finding in present study were similar to the work done by Brigham et al (13) and indicates that the medical advice of “next pregnancy being alright” might be misleading and a thorough evaluation is warranted in each loss.
Subsequent Pregnancy Outcome according to Maternal Age In Patients with Recurrent Pregnancy Loss

The association between age and abortion reflects both natural forces of selection and underlying biological mechanisms. In the present study, due to the early age at marriage and child bearing, majority of the patients were in the younger age group. Only two patients were aged 35 years and none of the patients was more than 35 years. On comparing the outcome of present pregnancy in each age group, more successful outcomes were seen in younger age group and the successful outcomes reduced with increasing age, decreasing to 50% in 31-35 years age group. The findings in present study were consistent with Brigham et al(13), Clifford et al(14), Nybo Anderson et al(15). Also, percentage of low birth weight, IUGR, pre eclampsia, Cesarean section, was noted more in older age women. Therefore, it can be concluded that age has a profound impact on pregnancy outcome.

Subsequent Pregnancy Outcome In Primary RPL And Secondary RPL

Patients with primary recurrent pregnancy loss, who did not have any successful pregnancy in the past, were observed to have a successful outcome in the present pregnancy in 74% of study population. This was lower than the outcome in patients with secondary pregnancy loss, who showed 87.5% successful outcome in present pregnancy. In patients with secondary RPL, who had a single successful pregnancy in the past followed by consecutive abortions, showed 85.5% success rates. Patients with more than one successful pregnancy in the past followed by consecutive abortions showed the most positive outcome in their present pregnancy. In Patients with bad obstetric history, 66.6% showed a positive outcome in the present pregnancy, however, IUGR, low birth weight and prematurity was observed to be higher in this group. Brigham et al, did not observe a significant difference in the outcome of the two groups. Regan et al (16), studied the influence of previous reproductive performance on risk of abortion in present pregnancy and concluded that a higher success rate was observed in patients with a history of previous live birth as compared to primary RPL patients. Similar observations were documented in the study by Jivraj et al(10).

However, the cause remains unexplained. Regan et al (16) suggests that though a past successful outcome does not exert a protective effect, but, a persistent lack of some factor, which would otherwise, allow a pregnancy to continue, might be responsible for recurrent miscarriages. Another reason which may explain this difference may be the psychological upset and anxiety that affects patients whose all pregnancies have ended in abortions, as recurrent abortions are hugely distressing for a couple.

Overall subsequent outcome After Intervention

In the present study, successful pregnancy outcome after intervention, was observed in 54 patients i.e. 77.1% of the study population. This includes full term as well as preterm births. Six patients suffered miscarriages again in study pregnancy, one had intrauterine demise, and in two patients baby died due to VLBW and prematurity (one had abruption and second patient had preterm delivery). The overall unsuccessful outcome of the present study was observed to be 12.8%. One patient did not conceive, while six ANC’s with > 20 weeks of gestation at the end of study period, account for the remaining 8.7% cases. Tulppala et al(17)
reported successful outcome in 62.5% and unsuccessful outcomes in 13.4% cases.

**Mode of Delivery**
Caesarean section was done in 6 patients i.e 10.5% of study population while 89.5% had vaginal birth. Indications for caesarean section being failure to progress in labour, fetal distress, IUGR, placental abruption, bad obstetric history, severe oligohydramnios and malpresentation.

**Obstetric Complications**
In the present study, obstetric as well as neonatal outcomes were observed. It was found that, gestational hypertension (blood pressure >140/90) occurred in 5.7%, pre-eclampsia in 5.7% which was further complicated by abruption in 3 patients and had devastating complications in the affected pregnancies, like IUD. Intrauterine growth retardation (birth weight <5th percentile for gestational age) was seen in 12.8%, multifetal gestation in 7%, severe oligohydramnios was noted in 8.7%, preterm birth in 18.5%, intrauterine fetal demise in 1.7%, one patient with gestational diabetes mellitus had macrosomic fetus (3.7 kg at 35 weeks gestation) while in 71.1% patients, no obstetric complication was observed. R.H.F. van Oppenraaij et al reviewed earlier literature and evaluated the impact of early pregnancy events and complications; which included recurrent pregnancy loss; as predictors of adverse obstetric outcome. According to the data collected a higher percentage of obstetric complications i.e. PIH, pre eclampsia, ante partum hemorrhage, preterm delivery, low birth weight and perinatal mortality and morbidity, was observed in patients who had recurrent miscarriages as compared to those who suffered single abortions. Study done by Bhattacharya et al (18), also revealed similar findings. Jivraj et al (10) observed obstetric outcome in RPL patients and compared them to the local obstetric population. He found the rate of preterm delivery, IUGR, caesarean section and perinatal mortality to be higher than those of the study population. However, no differences in the rate of hypertensive disorders and diabetes were observed between the two groups.

**Perinatal Outcome**
The perinatal outcome following management in all groups showed 71.9% RPL patients had term delivery in present study. 22.8% patients had preterm delivery. One patient had IUD following severe pre-eclampsia and abruption, in two patients, baby died due to prematurity and very low birth weight(<1500 grams). Overall, 5.3% patients had poor outcome. Nearly 40% of Preterm Neonates required NICU admission due to prematurity and low birth weight whereas other 60% needed only routine neonatal care. Amongst Term Neonates only 12.2% required NICU admission and 90% were shifted to mother side and given routine neonatal care.

**Conclusion:**
The present study was conducted in 70 cases of recurrent pregnancy loss patients in Rural Medical College and Hospital, Loni. The Mean age of patients in present study was 25.2 years, mean BMI was 23.7 kg/m2 and the mean number of abortions was 2.7. 77.2% were Primary RPL and 22.8% were secondary RPL. 72% cases had first trimester abortions while 28% had second trimester abortions. Advancing maternal age as well as previous unsuccessful pregnancies directly influence the outcome of next pregnancy. 91.1% cases with history of 2 abortions had successful subsequent pregnancy which decreased to 66.7% in patients with history of 4 abortions. Rate of Successful outcomes was more in younger age group and it reduced with increasing age, decreasing to 50% in 31-35 years age
group. One or more previous live birth have a positive influence on next pregnancy with 87.5% success rate, while previous pregnancies ending in abortions and a bad obstetric history had 74% and 66.6% success rates respectively. Overall successful outcome in subsequent pregnancy after intervention was 77.1% of which 71.5% were term deliveries. Obstetric complications observed among the study group included gestational hypertension, abruptio, severe oligohydramnios, IUGR, and prematurity. 20.4% neonates required NICU admission.

From our study we conclude that the knowledge of factors such as maternal age at conception, reproductive history, and number of miscarriages in a RPL patient is essential for the assessment of risk of abortion in next pregnancy. RPL patients should be carefully monitored in first trimester of next pregnancy as this is observed to be the most perilous time in such patients. Although the cause remained unexplained in 65% cases, a good outcome was observed even with supportive care.

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Above all, I thank Almighty God, by whose grace; we see the light of the day.

Tanya Pradhan

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