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Research Article

Evaluation of Causes of Recurrent Pregnancy Loss among Couples Attending a Tertiary Level Hospital of Dhaka, Bangladesh

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Abstract

Backgrounds and Aim: Recurrent pregnancy loss is a very distressing condition. Lots of couple with H/O RPL consult at infertility OPD. Proper evaluation and treatment as well as psychological supports can help to overcome the situation for these couples. My aim was to evaluation of causes of RPL.

Material and Method: This descriptive cross sectional study was conducted at BRB Hospitals Limited, a tertiary level hospital of Dhaka, Bangladesh from March 2019 to February 2021. Couple who came to Obs-Gyn department of this hospital with the complaints of two or more clinically proven pregnancy loss were included in the study. Total 84 patients were evaluated.

Results: Total 84 patients were included in the study. Highest percent of RPL was found among age group of 30 - 34 years (50%). Maximum patients came with 2 previous miscarriages 58.3% and lowest number was in more than 3 miscarriages 14.3%. Regarding causes of RPL, unexplained and APLS were same in percent, 25%. After proper evaluation and treatment, 29 patients conceived, 12 healthy baby delivered and 17 pregnancy is ongoing.

Conclusion: Recurrent pregnancy loss may end at a born of a healthy baby if proper evaluation and treatment is applied. Tremendous psychological support is essential part of treatment for these couples. But, unfortunately about 50% cases, cause remain unknown. If there is no treatment available, health care provider should provide at least tender loving care, which will improve the mental strength of these couples.

Keywords: *RPL; Unknown Etiology; APLS; Primary RPL; Secondary RPL*

Introduction

Pregnancy is a physiological change. But 15 - 35% of pregnancies may end up as abortion. Among all abortions less than 5% occurs in two and less than 1% occurs in three consecutive pregnancy loss [1]. Miscarriage is defined as the spontaneous loss of pregnancy RPL may be defined as three or more consecutive miscarriages occur before 20 weeks of gestation [21]. According to ASRM guideline RPL is a distinct disorder characterized by two or more documented clinical pregnancy losses excluding biochemical losses. (Not necessarily consecutive) [5]. ESHRE also supports in two or more pregnancy losses to define RPL [23].

Primary RPL is defined when a woman with RPL and no previous H/O pregnancy beyond the age of viability. Secondary RPL is defined as a woman with RPL and H/O pregnancy beyond the age of viability [2,3].

Etiology of recurrent pregnancy losses: There are lots of causative factor and sometimes unexplained RPL (Where no cause found) may occur. Common causes are:

1) **Epidemiological factors:** Maternal age and number of previous miscarriage are two independent risk factor for a further miscarriage. Chance of abortion is 40% after 3 consecutive RPL [4].

2) **Antiphospholipid syndrome:** Antiphospholipid syndrome is the most important treatable cause of RPL. It is seen 15% of women in recurrent miscarriages. It is first diagnosed in pregnancy in 10 - 30% case [22]. Antiphospholipid Ab causes inhibition of trophoblastic function and differentiation, activation of complement pathway and finally thrombosis of uteroplacental vessels [4,5].

Diagnostic criteria for antiphospholipid syndrome are:

- International consensus classification criteria for the antiphospholipid syndrome (APLS).
- APS is present if one of the following clinical criteria and one of the laboratory criteria are met.

Clinical criteria:

A) Vascular thrombosis.

B) Pregnancy morbidity:

1) One or more unexplained deaths of morphologically normal fetuses after the 10^{th} week of gestation by USG or direct examination of the fetus.

2) One or more premature birth of morphologically normal neonate before 34^{th} week of gestation because of eclampsia or severe PE or recognizes features of placental insufficiency.

3) Three or more unexplained consecutive spontaneous abortions before 10^{th} week of gestation with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria:

- Lupus anticoagulant present in plasma in two or more occasions at least 12 weeks apart.

- Anti-cardiolipin Ab of IgG and IgM in serum or plasma present in medium or high titer on two or more occasions at least 12 weeks apart.
- Anti beta2 glycoprotein-1 ab of IgG and or IgM (in serum or plasma in titer greater than 99th percentile) present on two or more occasions at least 12 weeks apart [24,25].

Genetic factor: Chromosomal anomaly occurs in aborted fetus is more than 50% in first trimester and 20% in second trimester [6]. This chromosomal defect may be parental origin or may spontaneously occur in the embryo with normal parenteral chromosome [9]. Possibility of abortion due to fetal aneuploidy decreases with subsequent pregnancy losses. ACOG recommends karyotyping of product of conception in women with 2 consecutive or 3 non consecutive miscarriages [8]. About 2 - 4% of RPL is due to parental chromosomal rearrangement, most commonly Balanced reciprocal or Robertsonian translocations and rarely inversions, insertions and mosaicism may found. For parental chromosomal abnormalities IVF may be needed with preimplantation genetic diagnosis and sometimes donor gametes may be used [11].

Anatomical factor: Prevalence of uterine anomaly in recurrent miscarriage vary from 1.8 to 37.6% [4]. Anatomical defect may be congenital (Septate, bicornuate and arcuate uterus) or acquired (Intrauterine adhesion, fibroids, polyp). Ultrasound specially 3D USG and transvaginal USG is essential tool to diagnose uterine pathology. Laparoscopy, HSG, Hysteroscopy, saline infusion sonography and MRI also sometimes needed to diagnose the pathology. Hysteroscopy will help in correction of the pathology [7,10,12].

A history of second trimester miscarriage associated with spontaneous rupture of membrane and painless vaginal delivery are typical feature of cervical incompetence. For cervical incompetence cervical cerclage should be given at 12 - 14 weeks or serial USG should be offered and when cervical length is less than 2.5 cm, then cerclage can be given [7].

Endocrine factor and metabolic factor: Luteal phase defect (LPD), Polycystic Ovarian Syndrome (PCOS), Diabetes Mellitus, Thyroid dysfunction, hyperprolactinemia are responsible for 17% to 20% of RPL. LPD is due to inadequate progesterone production by Corpus Luteum [11].

Disturbance in thyroid hormone, presence of anti TPO Ab in high titer hamper follicular development, sperm synthesis, fertilization and embryonic development and also responsible for RPL [14].

In case of PCO obesity, hyperinsulinemia, high LH, high androgen, high homocysteine and thrombophilia are associated factor in PCOS responsible for RPL [14].

Poorly controlled DM and high glycosylated Hb is responsible for RPL and birth of congenital abnormal baby [11].

According to ESHRE guideline routine prolactin test is not essential for RPL without any clinical suspicion. Elevated prolactin may causes anovulation but link with RPL is uncertain [16].

Immune factors: No clear evidence found regarding HLA incompatibility between couple, absence of maternal leucocytotoxic Ab or maternal blocking Ab with RPL. So, these tests are not routinely offered.

NK cells are found both in peripheral blood and uterine mucosa. UNK cells play very important role in trophoblastic invasion and angiogenesis and occupy 70% of all immune cells in feto maternal interface. Meta analysis by Seshadri., *et al*. showed that in case of RPL, peripheral NK cells number increased not the uterine NK cell. Testing of uNK cells and use of IVIG is still subject of research.

Cytokines control immune cells. T helper-1 (Th-1) cells are pro inflammatory and T helper-2 (Th-2) are anti-inflammatory. In normal pregnancy Th-2 takes upper hand and in case of RPL Th-1 cells are predominant. But more research is needed to find out link between cytokines and RPL [4,13,20,26].

Infective agent: Any bacterial or viral infection cause sporadic abortion not RPL. For RPL, infective agent has to persist in the genital tract, unable to detect and produce insufficient symptoms. TORCH infection doesn't fulfil the criteria and shouldn't be offered routine screening for RPL [4].

Thrombophilia: There are two types of thrombophilia: Inherited and Acquired. Usually, inherited thrombophilia is a causative factor for RPL at mid trimester. (Factor V Leiden and prothrombin gene mutation, Protein C, protein S and antithrombin deficiency). Acquired thrombophilia and RPL is a subject of research [4,5].

Ovarian reserve: Advanced maternal age and women with poor ovarian reserve have poor quality oocyte and number of oocyte also decrease. Ovarian reserve can be assessed by FSH, E2, AMH, Inhibin B, TVS for ovarian volume and AFC. Percentage of poor ovarian reserve is higher in women with RPL [14].

Male factor: Poor sperm quality can cause RPL. Increased DNA damage, increased reactive oxygen species, Y chromosome microdeletion, chromatin integrity of sperm may be altered in couples with RPL [14,20].

Environmental factor: Occupational and environmental exposure to hazardous chemicals, organic compounds, ionizing radiation, smoking, intake of alcohol, caffeine are causative factor for RPL. But further study is needed on these factors [11].

Unexplained: About 50% of patients will remain undiagnosed about the cause. Most effective therapy for unexplained RPL is proper antenatal counseling and psychological support [11].

Objective of the Study

- To find out cause of recurrent pregnancy loss.
- To find out outcome of treatment of RPL.
- To find out percentage of ongoing pregnancy and delivered baby after treatment.
- To find out age distribution of patients suffering from RPL.

Material and Method

This descriptive cross sectional study was conducted in BRB Hospitals limited, a tertiary level hospital of Dhaka, Bangladesh, between March 2019 to February 2021. Couples who came with the complaints of two or more documented clinical pregnancy loss were included in the study. Ectopic, Molar, biochemical pregnancy, H/O MR were excluded from the study. Both primary and secondary RPL were included. Total 84 patients were evaluated in this study. Detailed history, clinical examination and laboratory investigations were done. Chromosomal analysis of product of conception was not done, as because patients came after spontaneous abortions in the hope to prevent further miscarriage. ASRM and ESHRE guideline strongly suggest to evaluate after 2 miscarriage, as risk of miscarriage is 30% after 2 losses and 33% after 3 losses [17]. Detailed history was taken through a questionnaire after that clinical evaluation and investigations were done. Complete blood count, Hormone profile, Blood sugar, Trans vaginal sonography, HSG, Hysteroscopy, Screening for antiphospholipid Ab, Karyotyping of both partner, in special cases ovarian reserve testing and semen analysis also done. Chromosomal analysis of

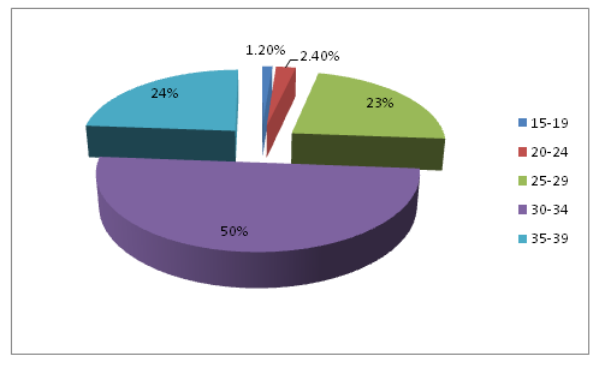
product of conception (came to this hospital after abortions) was not done. The women with RPL with treatable causes (medical/surgical) were treated according to ESHRE Guideline [3,15,18,19].

Results

Age distribution of RPL patients

Age Group	Frequency	Percent
15 - 19	1	1.2%
20 - 24	2	2.4%
25 - 29	19	22.6%
30 - 34	42	50%
35 - 39	20	23.8%
Total	84	100%

In this table age distribution is shown. Lowest percentage is found at age group 15 - 19 year and it is 12%, and maximum patients are with 30 - 34 year age group and it is 50%.



Pie Chart: *Age distribution of RPL.*

Number of abortions

Number of abortions	Frequency	Percent
2 Ab	49	58.3%
3 Ab	23	27.4%
> 3 Ab	12	14.3%
Total	84	100%

Above table shows that 49 patients H/O 2 abortions, 23 patients has 3 abortions and 12 patients suffered from more than 3 abortions.

Causes of RPL

Causes	Frequency	Percent
Unknown etiology	21	25 %
Anti-Phospholipid Ab	21	25%
Chromosomal abnormality of parents	5	6%
Endocrine	10	11.9%
Anatomical abnormality of uterus	11	13.1%
Poor ovarian reserve	5	6%
Abnormal semen parameter	2	2.4%
Mixed causes	9	10.7%
Total	84	100%

Above table shows that unknown etiology and APLS, both are at maximum position as cause of RPL and it is 25%. Abnormal semen parameter is only 2.4%.

Treatment outcome

Pregnancy outcome	Frequency	Percent
No pregnancy after treatment	55	65.5%
Ongoing pregnancy	17	20.2%
Healthy baby delivered	12	14.3%
Total	84	100%

After treatment total 29 women conceived, among them baby born in 12 ladies (14.3%), ongoing pregnancy in 17 ladies (20.2%) and 55 women (65.5%) yet not conceived.

Type of RPL

Type of RPL	Frequency	Percent
Primary	75	89.3%
Secondary	9	10.7%
Total	84	100%

Above table shows that no previous alive issue (Primary RPL) in 89.3% cases and previous H/O pregnancy beyond the age of viability in case of 10.7% cases (Secondary RPL).

Discussion

Pregnancy is very precious specially for infertile couple. In case of 15 - 25% of pregnancy sporadic abortion may occur [1]. Unfortunately, 3% pregnancy may end up as recurrent pregnancy loss [3]. It is very distressing condition and lots of couple suffer from chronic depression due to RPL. Usually, advanced maternal age is a causative factor for spontaneous abortion. Specially, miscarriage rate is higher if maternal age is more than 35 years and paternal age is more than 40 years [4]. But in my study, I found highest rate of RPL is in age group of 30 - 34 years and it is 50%. Next highest is 35 - 39 years age group and it is 23.8%.

According to Divya Pandey., *et al*. in case of 50%, cause of RPL is of unknown etiology [7]. In my study, I found 25% cases of RPL where no etiology is found.

According to RCOG guideline, APLS is responsible for 15% cause of RPL [4] and Hady EI Hachem., *et al*. showed that APLS causes RPL in 5 - 20% cases [9]. In my study, I found 25% RPL is due to APLS.

Holly B Ford., *et al*. described that RPL due to Endocrine and Anatomical factor is 15 to 20% and 10 to 15% respectively [11]. I found in this study that, endocrine etiology is 11.9% and anatomical deformity is responsible for 13.1%.

Shehnaz Sultana., *et al*. states that diminished ovarian reserve may be a causative factor for RPL [14]. In my study, I found that, 6% women are suffering from RPL due to poor ovarian reserve. Interestingly, all women were not from advanced maternal age group, I found younger women also have low AFC, diminished AMH and high FSH.

According to ASRM guideline, if semen parameter including morphology is normal, usually not responsible for RPL [5]. Abnormal semen parameter along with Sperm DNA fragmentation, Y chromosome microdeletion, sperm chromatin integrity are responsible factor for RPL [14]. In my country no available tests to assess sperm DNA damage, chromatin integrity or Y chromosome microdeletion. I found in my study that, in 2.4% case sperm parameter was very poor. Though, spontaneous pregnancy occurs, but there may be some molecular level abnormality which causes RPL.

In case of 10.7% I found more than one cause is responsible for RPL, so, it is classified as mixed cause.

Conclusion

Though RPL is not a health hazard but it is obviously very hazardous psychosocial issue. Mental depression, marital disharmony even divorce may occur due to this cause. Although, in 50% case no cause found for RPL. Remaining 50% cases, where cause may found but all causes are not treatable. But proper sympathy, empathy, cordiality will reduce some agony of this group of couple which will boost up their mental strength also. Treatable causes respond well with proper treatments. Couples with RPL sometimes visit at infertility center, and in case of abnormal chromosome of fetus or parental origin, IVF with PGD or PGS will help to achieve a healthy pregnancy.

Disclosure

The authors report no conflicts of interest in this work.

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