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Role of Hydroxychloroquine in Bad Obstetric History and Recurrent Implantation Failure - A Case Series

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ABSTRACT
Bad Obstetric History and Recurrent Implantation failure are very difficult situations encountered in clinical practice . Till date, in a majority of these cases no clear etiology is found and no definitive treatment exists. As a result it is a cause of great distress to both the couple and the clinician. Hydroxycholoroquine , initially used as an antimalarial agent has become the centre of interest in recent years due its various immunomodulatory actions. The same immunomodulatory action has interested researchers to explore its use in improving obstetric outcomes in patients with Bad Obstetric History and Recurrent Implantation Failure. In this case series we have explored the role of hydroxychloroquine in 7 such cases.

I. INTRODUCTION

Bad Obstetric History(BOH) and Recurrent Implantation Failure (RIF) are a cause of psychological , physical and economicaldistress to the suffering couple.

The term Bad Obstetric History is generally used to signify that a woman had adverse events in previous pregnancies. This could include miscarriage, stillbirth or any other adverse events[1].A pregnancy loss (miscarriage) is defined as the spontaneous termination of pregnancy before the fetus reaches viability[2]. The term therefore includes all the pregnancy losses from the time of conception until 24 weeks of gestation. As per ESHRE 2022 a diagnosis of Recurrent Pregnancy Loss (RPL) could be considered after the loss of two or more pregnancies[3]. Stillbirth as per WHO is defined as a baby who dies after 28 weeks of pregnancy , but before or during birth. It could be caused bya variety of conditions like deranged blood sugar levels , immunological conditions , high blood pressure , cervical incompetence and unknown causes.

Recurrent Implantation failure is defined by ESHRE 2023 as the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and/or interventions[4]. It can be caused due to a variety of causes like uterine anomalies , immunological causes , chronic endometritis and many unknown factors.

In around half of the cases of both bad obstetric history and RIF , standard examinations uncover no obvious reasons.There is currently no therapy whose effectiveness has been clearly demonstrated, even in the context of well known risk variables.

In 1955, Hydroxychloroquine , a Quinacrine derived molecule was first employed as an antimalarial drug. After its safety got well established , its anti-inflammatory and immunomodulatory effect got recognised. It was then used for treatment of various autoimmune conditions like SLE and Rheumatoid Arthritis[5].

PURPOSE OF STUDY: The purpose of this case series is to show the effectiveness of hydroxychloroquine in managing patients with bad obstetric history and recurrent implantation failure.

CASE DESCRIPTION :
7 Patients have been included in this case series who visited Institute of Reproductive Medicine and Women's Health , Madras Medical Mission Hospital between January 2020 to May 2023. Out of 7 patients , 4 had bad obstetric history , 2 had recurrent implantation failure and 1 was a known case of Systemic Lupus Erythematosus and Rheumatoid Arthritis.
Mean age of the patients was 30.3 yrs.

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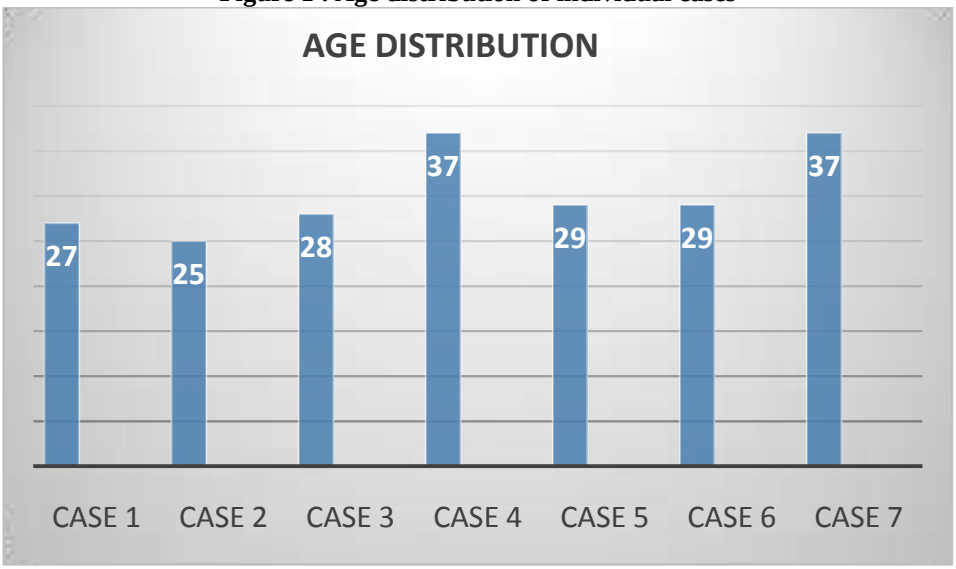
Figure 1 : Age distribution of individual cases



In patients with Bad Obstetric History (CASE1 TO 4) 3 had history of recurrent abortions and 1 had history of 2 Intrauterine deaths. Evaluation done for patients with Bad obstetric history is depicted in Table 1.

Table 1: Evaluation of patients with Bad obstetric history

INVESTIGATIONS	CASE 1	CASE 2	CASE 3	CASE 4
WIFE KARYOTYPE	Normal	Normal	Normal	-
HUSBAND KARYOTYPE	Normal	Normal	Normal	-
KARYOTYPING OF POC	Not done	Normal	Not done	-
HUSBAND SEMEN ANALYSIS	Normal	Normal	Normal	-
HUSBAND DFI	**HIGH**	12%	**HIGH**	-
CAVITY SCAN	Normal	Normal	Normal	Normal
THYROID AUTOANTIBODIES	Negative	Negative	Negative	Negative
BLOOD SUGAR	Normal	Normal	Normal	**HIGH**
APLA SCREEN	Negative	Negative	Negative	Negative

Among the 2 patients with Recurrent Implantation Failure (CASE 5 AND 6) one patient had 4 failed IUIs and 2 failed embryo transfers while the other had 3 failed embryo transfers. Evaluation done for patients with Recurrent Implantation Failure is depicted in table 2.

Table 2 : Evaluation of patients with Recurrent Implantation Failure

INVESTIGATIONS	CASE 5	CASE 6
WIFE KARYOTYPE	Normal	Normal
HUSBAND KARYOTYPE	Normal	Normal
HUSBAND SEMEN ANALYSIS	Normal	Normal
HUSBAND DFI	HIGH	11 %
CAVITY SCAN	Normal	Normal
THYROID AUTOANTIBODIES	Negative	Negative
BLOOD SUGAR	Normal	Normal
APLA SCREEN	Beta 2 MICROGLOBULIN POSITIVE	Negative

CASE 6 was also weakly ANA positive and CD3 positive.

MANAGEMENT:

Rheumatologist opinion was taken for all patients.All patients with Bad Obstetric History and 1 with Recurrent Implantation failure (Case 6) were diagnosed as Seronegative APLA Syndrome.Case 5 was diagnosed as Obstetric APLA Syndrome with Beta2 microglobulin positive.

All these patients were started pre-conceptionally or before embryo transfer on Tablet Hydroxychloroquine 400 mg and Tablet Aspirin 75 mg. Once the patient conceivedor after Embryo transfer was done ,patient was continued on Tablet Hydroxychloroquine 400 mg , Tablet Aspirin 75mg and Enoxaparin was added.

The diagnosed case of SystemicLupus Erythematosus and Rheumatoid Arthritis was already on Hydroxychloroquine and was advised to continue the same.

TREATMENT OUTCOME:

All 7 patients conceived on Hydroxychloroquine**.**Out of the 7 patients ,3 patients had Normal Vaginal Delivery , 3 underwent Lower Segment Caesarean Section and 1 resulted in a miscarriage. Average gestational age at delivery was 37 + 3 weeks .Average birth weight was 2.8 Kg.

II. DISCUSSION

In this case series Tablet hydroxychloroquine at a dose of 400 mg together with Tablet Aspirin 75 mg was started pre-conceptionally in patients with Bad Obstetric History and Recurrent Implantation Failure. It was found to be very effective in both scenarios.

Similar results were obtained in a Randomized Controlled Trial conducted by Abd Elhamid Mahmoud El Sayed et al studying ,whether Hydroxychloroquine has a role for Prevention of Unexplained Recurrent Miscarriage in which , they concluded that significant positive results were found with the orally administrated Hydroxychloroquine usage to increase the live birth rate in women suffering from recurrent miscarriages.[5]

H. Ghasemnejad-berenji et al in their study also found that the immunomodulatory effect of hydroxychloroquine was beneficial in patients with recurrent implantation failure[6].

In a study by Yan Dong et al exploring the role of Hydroxychloroquine in management of seropositive APLA Syndrome ,they came to the conclusion that it demonstrated a beneficial therapeutic effect[7]. Jamilya Khizroeva et al in their study explored the role of Hydroxychloroquine in patients with APLA syndrome in whom the anticoagulation therapy alone was not found to be very effective and they came to the conclusion that Hydroxychloroquine looks promising as a treatment alternative in these patients[8].

III. CONCLUSION

Orally administrated Hydroxychloroquine usage can improve the live birth rate in women suffering from Bad Obstetric History and Recurrent Implantation Failure , likely due to its potential anti-inflammatory and immunomodulatory effects. Larger studies are required to confirm its effectiveness and establish clear guidelines regarding its usage to improve obstetric outcomes.

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