International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 11 (C); November 2019; Page No.20494-20497
DOI: http://dx.doi.org/10.24327/ijcar.2019.20497.4006

Research Article

TO STUDY THE EFFECT OF TRANEXAMIC ACID IN EARLY PREGNANCY BLEEDING IN POST IVF PREGNANCIES: A PROSPECTIVE OBSERVATIONAL STUDY

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A R T I C L E I N F O

Article History:
Received 12th August, 2019
Received in revised form 23rd September, 2019
Accepted 7th September, 2019
Published online 28th November, 2019

Key words:
IVF pregnancies, Early Pregnancy bleeding, Tranexmic Acid

A B S T R A C T

Bleeding in early pregnancy is a common. It has been linked with adverse obstetric outcome. Inadequate angiogenesis, inflammation of chorionic tissue, defective placentation and mechanical separation of the developing placenta are some of the mechanisms described. Traditionally progesterone has been prescribed in such cases to augment the luteal support. Post IVF (in vitro fertilization) pregnancies are usually on progesterone support in early pregnancy. Tranexamic acid is a hemostatic agent which binds lysine sites on plasminogen and act as competitive inhibitor of plasminogen activation thereby preventing fibrin degradation. Its safety and effectiveness have been established in various clinical scenarios. Use of Tranexamic acid in post IVF pregnancies with threatened abortion arrested the bleeding rapidly and found to be safe and effective. Study can be a basis for other studies with more representative sample and better study design.

INTRODUCTION

Vaginal bleeding of intrauterine origin in early viable pregnancy is known as threatened abortion. It complicates 16-25% of the pregnancies after spontaneous conception (1).

Sub chorionic blood collection can be seen in 18-20% cases of threatened abortion on ultrasonography (2).Threatened abortion and sub chorionic hemorrhage have been linked with adverse obstetric outcome like fetal miscarriage, preterm labour, placental abruption, placenta previa, fetal growth restriction(3).Defective placentation, inadequate angiogenesis and chronic inflammation of decidua have been implicated as cause for bleeding in early pregnancy. Premature exposure of placental sinusoids to high oxygen tension with early pregnancy hemorrhage results in oxidative stress leading to defective placentation and poor obstetric outcome (4).Sub chorionic blood collection causesmechanical separation of placenta from the decidua and adversely affects pregnancy outcome (5).

Post IVF pregnancies are at high risk for adverse outcome (6). The incidence of bleeding in early pregnancy, miscarriage, low birth weight, prematurity and low Apgar scores is more in post IVF pregnancies. Progesterone support is added virtually in all post IVF pregnancies more so in the first trimester. Threatened abortions with or without sub chorionic collection have been empirically treated with natural or synthetic progestins without clear evidence (7).

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Treatment modalities targeted to arrest sub chorionic bleeding are likely to be helpful in limiting the size of bleed, oxidative stress and degree of placental separation. Tranexamic acid has been used over decades as an antifibrinolytic agent. It is an analogue of amino acid lysine. It acts on the lysine sites on plasminogen molecule and prevents degradation of fibrin, thereby stabilize the clot to exert haemostatic effect. It is a category 'B' drugin the pregnancy as per FDA classification and is on the World Health Organization's List of Essential Medicines(8).

Safety and effectiveness of the drug has been established with its vast use in surgical and obstetric fields. Tranexamic acid has been tested primarily in third trimester and during cesarean sections to prevent post partum hemorrhage with promising safety and effectiveness, however the studies of its use in early pregnancy hemorrhage are limited in number.

IVF pregnancies are associated with emotional vulnerability and risk for depression. The chances of achieving a successful second pregnancy after first pregnancy loss are less in sub fertile couples. Both first and early second trimester bleeding is encountered more frequently in IVF pregnancies. These patients are usually on progesterone support at the time of bleeding. Treatment with haemostatic agents like Tranexamic acid is likely to arrest the bleeding and improve the obstetric outcome. Aprospective observational study was carried out on fifty-two cases in first and early second trimester of pregnancy with active vaginal bleeding to determine haemostatic effectiveness of Tranexamic acid treatment in arresting the bleed.

Aims and Objectives

AIM

To study the effect of Tranexamic acid treatment in post IVF patients presenting with threatened abortion in first and early second trimester of pregnancy.

Primary Objective

1. To study the haemostatic effectiveness of Tranexamic acid in early pregnancy bleeding

Secondary Objective

1. To study the antenatal complications in treated population
2. To study the obstetric outcome of treated population

MATERIAL AND METHOD

Study design
Prospective observational study
Study population:
Post IVF pregnancies in first or early second trimester (less than 24 weeks POG)
Duration of study:
18 months

Inclusion Criteria

- Post IVF pregnancy with active vaginal bleeding in first or early second trimester
- Viable pregnancy (presence of fetal cardiac activity) on ultrasonography

Exclusion criteria

- Spontaneously conceived pregnancies
- Non-viable early pregnancy
- Uterine anomalies
- Coagulation disorder or patients on anticoagulants
- Local cause for vaginal bleeding
- Patients with spotting p/v or incidentally detected subchorionic bleeds on USG
- Heterotrophic pregnancy
- Missed or inevitable abortion
- Known cases of cardiac, renal, hepatic disease, seizure disorder, sickle cell anemia and acquired color blindness
- Hypersensitivity to Tranexamic acid

Treatment protocol

Patients conceived following IVF (fresh or frozen embryo transfer), meeting inclusion and exclusion criteria, who presented with active vaginal bleeding in first or early second trimester of pregnancy were treated with an injection of Tranexamic acid 1 gm iv infusion over 15 min followed by oral tranexamic acid 500mg eight hourly for 48 hours. Dating and viability of pregnancy was confirmed by ultrasonography at presentation. Sub chorionic hemorrhage when present was measured and documented. Standard vaginal pads were used and preserved till observed by obstetrician to assess blood loss. Repeat ultrasonography was done after 48 hours. Progesterone support was continued. Patient was followed up during antenatal period, delivery and a week post-partum.

RESULTS AND OBSERVATIONS

Total of fifty-two patients presenting with early pregnancy bleeding, meeting inclusion and exclusion criteria were selected. Demographic details, cause of infertility and ultrasonography findings are tabulated as Table- 1, Table-2 and Table-3 respectively.

Table 1 Demography

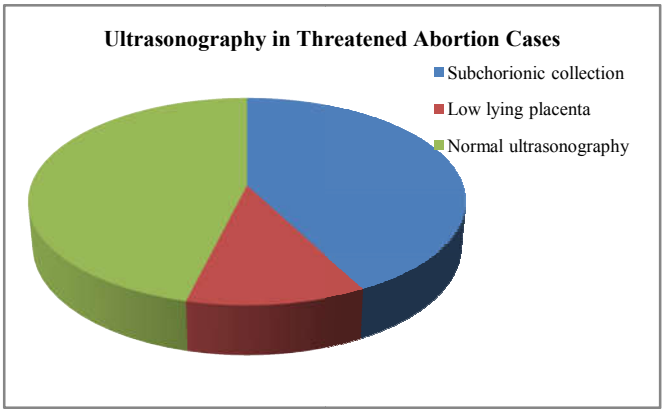
Mean maternal age	**32.7 yrs**
Average duration of infertility	06 yrs 09 months
Primary infertility	32
Secondary infertility	20
Singleton pregnancy	29
Multiple pregnancy	22+1

Table 2 Cause of infertility

Male factor	**14**
Female factor	28
Both male and female factor	8
Unexplained infertility	12

Table 3 Subchorionic collection on ultrasonography

Sub chorionic bleed present	**22**
Low lying placenta	6
No sub chorionic collection and normally located placenta	24



USG in Threatened abortion Figure 1

All selected patients were given Tranexamic acid treatment as per institutional treatment protocol. Active bleeding stopped in all patients within two hours after giving Tranexamic acid infusion. Most patients changed two standard fully blood soaked pads in first two hours but thereafter changed only single pad in next twelve hours. Color of the blood also changed to dark brown by the next day. Bleeding stopped in all the cases after 48 hours of treatment. Fetal viability was confirmed again after 48 hours by ultrasonographybefore discharge.

Antenatal Complications

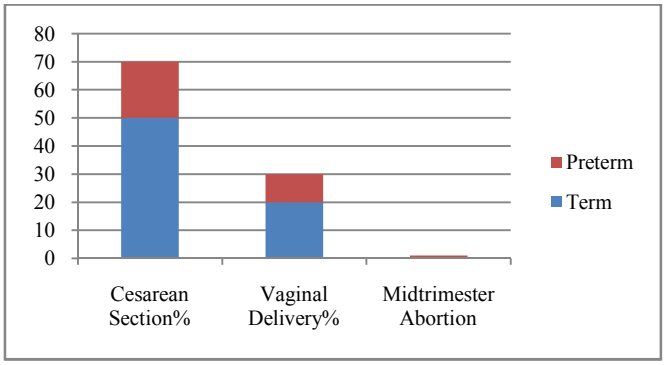
Table 4

Gestational diabetes mellitus	**16**
Pregnancy induced hypertension	12
Fetal Growth Restriction	6-singleton pregnancies 4-twins
Midtrimester abortion	01 (20 weeks)
IHCP	2
Placenta Previa&Abruption	2& 0
PPH (blood loss >500ml in normal and >1000ml in cesarean delivery)	2 Both during CS not requiring blood transfusion.

Mode of delivery

Table 5

Vaginal (Term, >=37 weeks)	15+1(twin)
Vaginal (Preterm, <37 weeks)	5(four singleton pregnancy, one-twins)
Cesarean section(Term, >=37 weeks)	23
Cesarean section(preterm, <37 weeks)	7



Mode of delivery **Figure 2**

Neonatal complication

Table 6

Low birth weight	12
NICU admission	8
TTN	2
Neonatal hyperbilirubinemia	4
Low Apgar score	2

Antenatal complications, mode of delivery and neonatal complications are tabulated in Table 4,5 and 6 respectively.

DISCUSSION

Bleeding in early pregnancy is common. Threatened abortions have been treated with progesterone support without clear evidence.

Tranexamic acid is *'trans-4-(aminomethyl) cyclohexanecarboxylic acid'* and an analogue of amino acid lysine. It binds lysine sites on plasminogen and act as competitive inhibitor of plasminogen activation thereby preventing fibrin degradation. It has no effect on the platelet count, coagulation factors and coagulation time in therapeutic concentrations up to 10mg/ml of blood. It crosses placenta and present in breast milk. Drug is available in oral as well as injection form. It does not bind albumin and excreted primarily unchanged in urine with half life of two hours. Up to 90% of the drug is excreted in 24 hours. Gastrointestinal disturbances are common. Allergic dermatitis, giddiness, and hypotension have been reported occasionally. Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis), convulsion and visual disturbances have been reported very rarely.

The drug has been used widely over decades in surgical practice as haemostatic agent and has been shown to be both safe and effective. CRASH-2 trials (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage) have provided quality evidence that it decreased the blood loss and mortality in trauma patients which led its inclusion in the 19th WHO list of essential drugs.(9)

It has also been used in the obstetric practice. It has been recommended as one of the strategies to reduce the use of blood products in obstetrics by preventing blood loss. In a meta-analysis of 25 RCT with 4747 participants, Tranexamic acid has been found to be both safe and effective in prevention of post-partum hemorrhage.(10) A systematic review of 29 RCT with 10 488 participants have shown no increase in thrombotic complications like myocardial infarction, pulmonary embolism, stroke or deep vein thrombosis.(11) The CRASH-2 trial on use of Tranexamic acid in Trauma patients has shown decrease in mortality without any increase in thrombotic complications. (12)

Pregnancy is a hyper coagulable state and the chances of thrombotic complication are highest in the immediate post-partumperiod. (13) Number of studies have established its effectiveness; however, none has shown an increase in thromboembolic complications in pregnancy with the use of Tranexamic acid (14-17)

Vaginal bleeding complicates 25% of pregnancies before 20 weeks & half of these result in miscarriage. (18)Bleeding in early pregnancy is associated with adverse obstetric outcome. Presence of subchoroidal hemorrhage doubles the chances of pregnancy loss.(19) Kalinka J *et al* found increase miscarriage, growth restriction and preterm deliveries in patients with threatened abortion.(20) Premature perfusion of the intervillous space and resultant oxidative stress, secondary mechanical effects of the hematoma and defective trophoblast invasion with impaired angiogenesis are the likely mechanisms of SCH. (21-22)

Progesterone is a steroid hormone secreted by the corpus luteum in early pregnancy and by placenta in later gestation. It brings secretary changes in endometrium, support implantation and pregnancy. It has been used in natural as well as synthetic forms empirically to treat threatened abortion without clear evidence and is category B drug in pregnancy. (23)

Patients with IVF pregnancies constitute a separate set of patients with different clinical profile. They are emotionally vulnerable and at risk for depression. (24) They are usually nulliparous, have advanced age and higher chances of having multiple pregnancies. These patients are at higher risk for developing antenatal obstetrical complication even with singleton pregnancies. (25) GDM is 1.99 times, gestational hypertension is 2.58 times, preeclampsia is 1.49 times, IHCP is 2.8 times, placenta previa is 2.2 times, placental abruption is 5 times, PPROM is 3 times and PPH is 2.7 times more common. Also, preterm labour, low birth weight, small for gestational age and low Apgar scores are more common on matched singleton pregnancies. (26) Both progesterone and tranexamic acid are category B drugs in pregnancy. Though the progesterone is used frequently for pregnancy support and to treat bleeding in early pregnancy empirically, obstetric use of tranexamic acid has been primarily confined to late pregnancy during cesarean section despite adequate evidence on its safety and effectiveness across surgical fields.

Tetruashvili NK *et al*, studied the effectiveness of Tranexamic acid in patients with threatened abortion. Authors concluded that Tranexamic acid treatment during early pregnancy arrested the bleeding more rapidly and helped in prolonging the pregnancy. (27)

Limitations of the study

In the present study, Tranexamic acid treatment appears to be safe and effective in arresting early pregnancy bleeding. The study is limited by its nature being observational study. The study population is post IVF pregnancies which are usually

complicated with several other factors and not a true representative of general population. These patients are already on progesterone and sometimes on combined estrogen and progesterone support which further limit the scope of study. However, study can be basis for further studies with better study design and sample population representing normal population for making any recommendations.

CONCLUSION

Though the safety and effectiveness of tranexamic acid in trauma and prevention of PPH was established, there are very few studies in literature in the use of haemostatic therapy in early pregnancy despite category B drug.(27) The sample size is small, study population is not a representative of general population and study design is weak, however the study enforces the safety and effectiveness of Tranexamic acid in early pregnancy hemorrhage. The study provides a base for larger studies with better study design.

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