Study of Fresh Versus Frozen Embryo Transfer with Reference to Early Pregnancy Loss

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Abstract

Background: Etiology of Increased rate of early abortions associated with pregnancies happened after In Vitro Fertilisation are not understood fully till date. 'Freeze all embryos' is a new dictum of improving the overall success of In Vitro Fertilisation,although it's effect on early pregnancy loss is controversial in existing literature .So many studies stated that vitrification and thawing process although improves the positive pregnancy rate but cause early pregnancy losses after implantion, but other studies contradict it. Hence in present study we wish to find out the difference of early pregnancy demise in frozen thaw embryo transfer cycles in comparison to fresh embryo transfer cycle.

Trial Design: This is a cross sectional study which will be conducted in Wardha test tube baby centre, Acharya Vinoba Bhave Rural Hospital.

Method: 20 consecutive women conceived after In Vitro Fertilisation, either Fresh or Frozen embryo transfer and will be followed up further for rate of early abortions amongst them.

Expected Outcomes: Frozen embryo transfer cycles may have more chances of successful clinical pregnancies at 6-7 weeks of gestational age, but later on may result in early pregnancy losses.

Keywords: *Frozen, Embryo Transfer, Early Pregnancy Loss.*

Introduction

Presently frozen embryo transfer is one of the most recommended procedures in advanced treatment of infertily. As the success of In Vitro Fertilisation, is still limited in spite of so many advancements in all the fields of reproductive biology, frozen embryo transfer is a viable alternative to fresh embryo transfer considering that the endometrium and ovaries of fresh stimulation cycles are not properly prepared for implantation[1]. In frozen embryo transfer there could be better control of both endometrium and ovaries hence pregnancy rates are proposed to be increased and perinatal outcomes should be better than fresh embryo transfer, In few studies the rate of clinical abortion and biochemical pregnancy was reported around 20% after frozen embryo transfer [2].

Previously clinical indications for frozen embryo transfer (cryopreservation) were to help the cancer patient undergoing treatment, patients who have premature ovarian failure, to overall delay the fertility procedure for so many social factors[5].

Now days all freeze strategy is almost replaced the standard fresh assisted reproductive technique hence frozen embryo transfer is an important part of assisted reproductive technology. Previous studies suggested

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that procedure of frozen embryo transfer reduces the number of transferred embryos as well as also reduces the risk of multiple pregnancies, risk of Ovarian Hyper Stimualation Syndrome and ectopic pregnancies[1].

Elective frozen embryo transfer has been shown higher live birth rate than a fresh embryo transfer amongst the women with poor ovarian reserve or polycystic ovarian syndrome[4].

In spite of many advantages of vitrification and slow thawing process in frozen embryo transfer, there is a rising concern of increased number of early pregnancy losses and more chances of aneuploidy and abnormal genotype associated with it.

There is some controversy regarding the early positive pregnancy rates due to better implantation versus take home baby outcome of patient undergoing with healthy babies in frozen embryo transfer.

With this background, we would like to conduct the present study to compare the early pregnancy losses and their associated factors in fresh versus frozen embryo transfer.

Aim: This study aimed to find out the rate of early pregnancy losses in frozen and fresh embryo transfer cycles of in vitro fertilisation.

Objectives:

1. To compare serum β–Human Chorionic Gonadotrophins level on day 14th in post embryo transfer in fresh and frozen embryo transfer women.
2. To confirm presence or absence of sac in both the groups.
3. To compare the appearance of cardiac activity and other early foetal parameters in both groups
4. To compare early pregnancy losses in both the groups.
5. To compare late complications of pregnancy in both the groups.
6. To compare final outcome of pregnancy in both the groups.

Method

Study Design: Cross sectional study

Setting and Location: The study will be conducted in the rural area of Central India which caters up to 30 kms surrounding area.

Wardha Test Tube Baby Centre is the only centre providing advanced infertility care in whole of the district. This centre is associated with tertiary care fully equipped rural hospital

In Vitro Fertilisation lab, Acharya Vinoba Bhave Rural Hospital, Sawangi.

Period of recruitment and relevant dates will be decided before planning the stimulation protocol for these infertile women that is June 2020 onwards for 6 months and exposure will be for 10- 12 days.

The Follow up will be up to 12 weeks after conception

Analysis and Data Collection will be done after 9 months of the study. Subjects will be explained about the nature and purpose of the study after assuring confidentiality and taking informed consent the details of the patient will be entered in data forms the proforma of the subjects will be preserved comprising of demographic details, past medical, surgical and comorbid conditions. Personal and family history which might affect early pregnancy losses.

Participants:

Inclusion Criteria:

- Couples suffering from primary/secondary infertility fulfilling the indications of In Vitro Fertilisation .
- Patient with history of pregnancy loss with fresh embryo transfer.

Exclusion Criteria:

- Patient with abnormal semen parameter.
- Patients not giving consent for research.
- Patients having uterine agenesis.
- Patients not fit for In Vitro Fertilisation having viral infections like Human Immune deficiency Viral disease, Hepatitis B S Antigen etc.
- Patients with known history of early pregnancy losses.

Sources: Infertility patients at outpatient department of Acharya Vinoba Bhave Rural Hospital for seeking In Vitro Fertilisation treatment.

Method of Selection: All the women whose beta human corionic gonadotrophin, will come positive after 14 days of embryo transfer.

Outcome Parameters:

Primary Outcome:

1. To compare beta human corionic gonadotrophin level on day 14th in post embryo transfer in fresh and frozen Embryo Transfer women. [COMPARABLE]
2. To confirm presence or absence of sac in both the groups. [COMPARABLE]
3. To compare the appearance of cardiac activity and other early fetal parameters in both groups [EXPECTED TO BE LESS IN NUMBER IN Frozen Embryo Transfer]
4. To compare early pregnancy losses in both the groups.

Secondary Outcome:

1. To compare late complications of pregnancy in both the groups.
2. To compare final outcome of pregnancy in both the groups.

Predictors:

1. Abdominal pain after gestational sac visibility
2. Bleeding per vaginum after gestational sac visibility

Confounders:

1. Advanced Maternal Age
2. Ante Mullerian Hormone
3. Number of embryos formed

Diagnostic Criteria:

Signs and symptoms of inevitable abortion.

Bias:

1. Blinding is not possible because of cost and time duration.
2. Method bias.
3. Confounding bias.

Study Size: 8-15 cycles per month are carried out in Wardha Test Tube Baby Centre, Out of which 60 % are self stimulation cycles 70 % of In Vitro Fertilisation cycles will suit to eligibility criteria considering dropout rate So average comes out to be 4-5 patients per month

Sample size Calculation:

$N = \aleph^2 * N * p(1-p)/C^2(N-1)+\aleph^2 p(1-p)$

Total population = N=20 during 12 months

$\aleph^2$ = Chisquare value for 1 degrees at some desired probability level. This is 3.84 at 5% level of significance.

P = 50% proportion

Q = 100-p

= 50

C = Confidence interval of the one choice (95% CI)

= 0.05

N = 3.84*20*0.5*0.5

$(0.05)^2$ *24+3.84*(0.5*0.5)

= 23.52 = 19

Quantitative Variables:

Not applicable

Statistical Method: The statistical analysis will be carried out using the SPSS 22 software package (SPSS Inc., Chicago, IL).

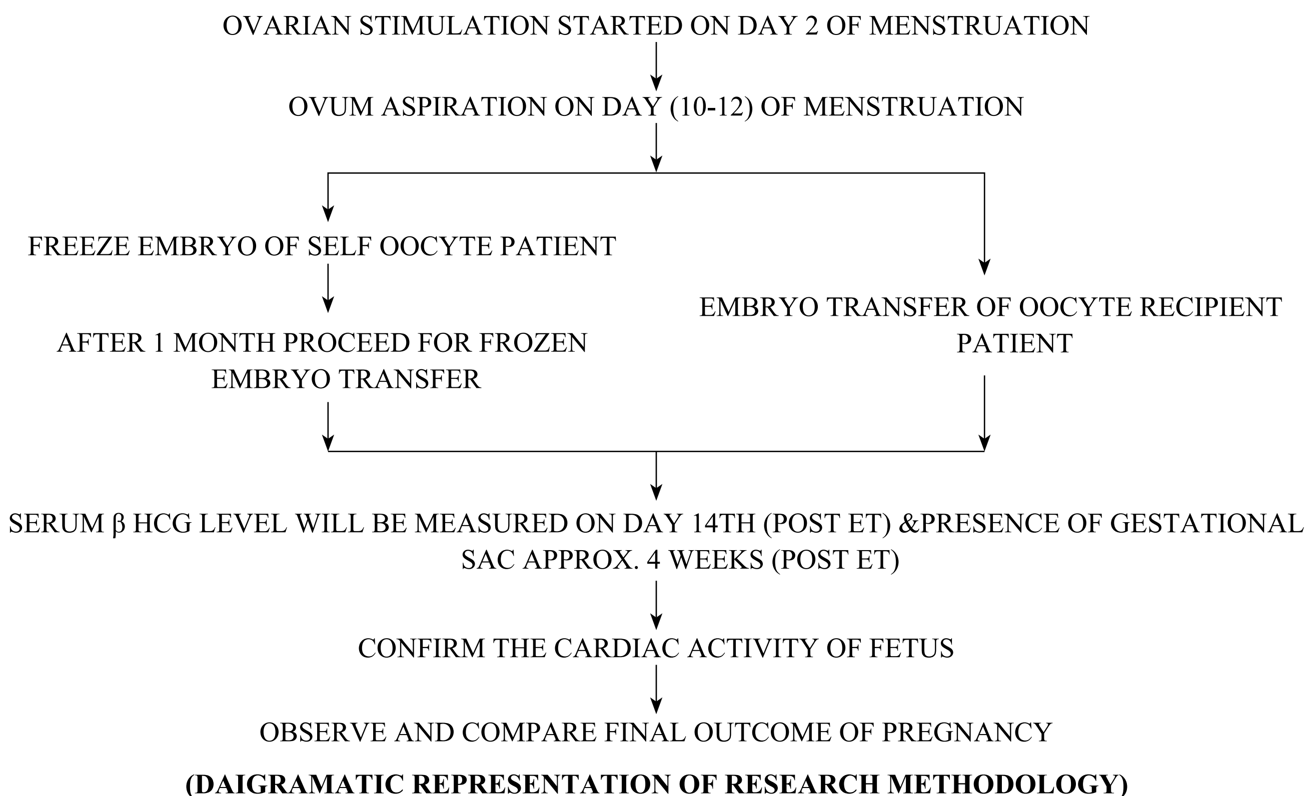
The method used is Chi Square test

Expected Results:

1. The β-HCG level on day 14th in post embryo transfer in fresh and frozen Embryo Transfer women would be COMPARABLE without stastical significance.
2. Presence or absence of gestational sac in both the groups would be COMPARABLE without stastical significance.
3. The appearance of cardiac activity and other early fetal parameters in both groups is EXPECTED TO BE LESS IN NUMBER IN Frozen Embryo Transfer cycles.
4. Early pregnancy losses may be more in Frozen Embryo Transfer groups.

Secondary Outcome:

1. The late complications of pregnancy would be COMPARABLE without stastical significance in both the groups.
2. The final outcome of pregnancy would be COMPARABLE without stastical significance in both the groups.



(DAIGRAMATIC REPRESENTATION OF RESEARCH METHODOLOGY)

Discussion

Hyper stimulation of ovaries in In Vitro Fertilisation is started to make gonadotropins level in the body at supraphysiological level which may influence the genetic makeup of oocytes and subsequently the embryos formed, so also reduce the endometrial receptivity for transferred embryos may be leading to failure of In Vitro Fertilisation treatment, hence by transferring the embryo in frozen cycle may lead body to come to normal endocrinal status and may improve the success of In Vitro Fertilisation by restoring the endometrial receptivity and selecting genetically normal embryos after thawing. Whether combined effect of both may increase or reduce the early pregnancy losses after successful In Vitro Fertilisation treatment will be studied .With this background we wish to conduct this study the pregnancy rate in frozen-thawed embryo transfer cycles is usually lower than that of fresh transferred embryos.[1]

There was an increased risk of loss after frozen Embryo Transfers versus fresh among women younger than 38 years in a study done by Hipp et all. [2]

In contrast to fresh cycle, women who received frozen cycle embryo had a significant increased risk of early miscarriage ($P < 0.001$), while frozen cycle was linked with lower risk of late miscarriage ($P = 0.045$) according to Lingminet all. [3]

According to study done by Zhang B et al. the risks of gestational diabetes mellitus, preterm birth, and small for gestational age were comparable between the frozen and fresh embryo transfer groups in both singleton and twin births. However, singleton infants born after frozen embryo transfer were more likely to be large for gestational age (25.2% vs. 17.5%; relative risk 1.44, 95% confidence interval 1.01-2.07, P=.044) than those born after fresh embryo transfer. [4]

In a study done by Basirat et all however,no significant differences between biochemical pregnancy rate (23% versus 18.8%, OR 1.301; 95% CI .95-1.774), gestational sac (95.6% versus 100% in Frozen Embryo Transfer, OR 0.60; 95% CI 0.54-0.67), and fetal heart activity (87.2% versus 93.6% OR .46; 95% CI .16-1.32) in fresh embryo transfe and Frozen Embryo Transfer cycles, respectively. P< 0.05 was considered statistically significant for all measures.[5]

Apart from fresh and frozen transfer, the study done by A Kaluarachchia stated that The success rate was analysed according to the duration of embryo freezing.

This showed a gradual decline in the implantation rate according to the duration of freezing.[6]

There was an increase in the risk of obstetric complications in pregnancies resulting from Frozen Embryo Transfer when compared to those emerging from fresh embryo transfers according to Roque et all.[7]

Ethical Clearance: Taken from institutional ethics committee.

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Conflict of Interest: Nil.

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