



Title of Project: GnRH Agonist at Embryo Transfer

Principal Investigator: David Kulak, MD

Funding Source(s): Maimonides Self-Funded

1. Purpose/Specific Aims

The purpose of this study is to investigate the potential benefit of GnRH as an adjunct for in-vitro fertilization (IVF).

1.1 Objectives

We hope to demonstrate a significant difference in pregnancy and live birth rates in IVF patients who receive a GnRH agonist (Lupron) prior to embryo implantation.

1.2 Hypothesis

If a GnRH agonist is administered at the time of embryo transfer, then the success rate of pregnancy and live birth will be greater than the standard-of-care, which does not utilize this medication.

2. Background and Significance

During IVF cycles, an embryo is generally placed into the uterine cavity between 3 and 5 days after fertilization in a laboratory. For a successful pregnancy to take place, that embryo must then implant in the properly primed and staged endometrium, which subsequently must continue to develop to accommodate the growing and maturing embryo and soon-to-be fetus. This process is normally regulated by hormonal interactions between the fetal, endometrial and luteal tissue. It has been found that after embryo transfer additional support for the endometrium with progesterone improves implantation and, thus, live birth rates in IVF cycles (Van der Linden, Cochrane 2011). Recent data has shown that additional supplementation with a single administration of a GnRH agonist around the time of embryo transfer may further improve these rates (Oliveira, RepBiolEndo 2010; Van der Linden, Cochrane 2011, Ata 2008, Brigante 2013, Isik 2009, Tesarik 2006, Inamdar 2012, isikoglu 2007, Qublan 2008).

3. Research Design and Methods

This study is a randomized clinical trial. It will be a double-blinded, placebo-controlled study. On the day of embryo transfer (5-6 days after a fresh egg retrieval and on the sixth day of progesterone administration in a frozen embryo transfer cycle), patients will receive either

a single injection of 1mg of Lupron or an identical placebo injection. Patients undergoing day 3 embryo transfers will not be eligible and will not be randomized.

Randomization scheme will be computed via a computerized program accessible at randomization.com. Randomization will be in 22 blocks of 20 patients. There will be two separate randomizations, one for fresh embryo transfers and the other for frozen embryo cycles. Sequential cards with randomization allocation will be placed in doubly sealed, opaque envelopes. A single sheet confirming eligibility status and confirmation of the presence of the signed informed consent will be in the first envelope. The second envelope will be opened after there is confirmation that the patient is eligible and consented. This envelope will have a card stating the group the patient has been assigned to and blank spaces designated to record patient information. This card will be completed by the study staff and saved for reference purposes. The card will state the group that the patient was randomized to, date of embryo transfer, patient medical record number, name, and cycle type. There will also be a logbook to record the information and medication lot numbers.

Injections will be prepared at the time of randomization by a member of the study staff, and they will be administered by the clinical RN who will not know its contents. The clinical staff assessing and planning care of the patient (attending physicians and nurses) will not know the contents of the syringe (either Lupron 20IU or Saline).

3.1. Duration of Study

The study will last two years.

3.2 Study Sites

All embryo transfers are performed at the Maimonides-affiliated, Genesis Fertility office located at 6010 Bay Parkway, Ste. 501 in Brooklyn, NY. This will be the only site for the study.

3.3 Sample Size Justification

Based on an alpha error of .05 and power of .80, with an absolute increase in LBR of 15% (consistent with earlier studies, and an overall LBR per transfer of 39.2% - from Society of Assisted Reproduction Technologies data) we will need to enroll 352 patients (176 in each group) to reach statistical significance. In order to account for attrition and the exclusion of patients moved to day 3 (earlier embryo transfer for poor embryo development), we will anticipate 20% dropout and plan to enroll 440 patients, 220 in each arm.

3.4 Subject Selection and Enrollment Considerations

3.4.1 Inclusion Criteria

Women undergoing IVF/ICSI or frozen embryo transfers (FET) between the ages of 18 and 40 years old will be included.

3.4.2 Exclusion Criteria

Patients with day 3 embryo transfers will be excluded.

3.4.3 Subject Recruitment

Subject recruitment will be from our clinic population and patients that contact us from clinicaltrials.gov. Flyers with study information will be posted in the waiting room of our offices:

- 6010 Bay Parkway, Ste. 501, Brooklyn, NY 11204
- 808 Eight Ave., Brooklyn, NY 11215
- 1855 Richmond Ave., Staten Island, NY 10314
- 1175 West Broadway, Suite 24, Hewlett, NY 11557

Additional flyers will be posted at Maimonides Medical Center, where physicians have admitting and operating privileges, pending authorization from the hospital.

3.4.4 Consent Procedures

Patients will be consented to the study any time between initiation of treatment until, and including, the day of embryo transfer. The study will be explained to the potential subject by a member of the research staff (research nurse or fellow) and not the treating physicians. The consent will be read and questions will be answered. If she wishes to enroll, the subject will sign the consent form. The study staff obtaining consent will also sign and date the consent form, and a copy will be given to the subject.

3.4.5 Subject Costs and Compensation

Patients will not be reimbursed for their inclusion in the study, nor will they be charged for experimental medications. The study will cost approximately \$20,000, due mostly to the expense of the Lupron injection. We anticipate receiving funding in the form of a grant from ASRM, the American Society for Reproductive Medicine.

3.5 Chart Review Selection

N/A

4. Study Variables

4.1 Independent Variables or Interventions

The standard of care for patients who undergo embryo transfer is to administer luteal phase hormonal support in order to prime the uterus for implantation. The supplementation generally consists of hormones in different forms that are administered parenterally, vaginally, orally, and/or transdermally. This supplementation generally continues until about the eighth week of pregnancy in fresh embryo transfers and until the 11th week in frozen cycles (patients who use frozen eggs). Our study intervention will be a one time subcutaneous injection at the time of embryo transfer. Patients will receive either a single dose of a short-acting GnRH agonist (Lupron) or a single injection of subcutaneous saline as a placebo.

4.1.1 Drug or Device Interventions

A single dose of Lupron 20IU (0.2 mL) will be injected subcutaneously. The placebo will be a 0.2 mL subcutaneous injection of normal saline.

4.2 Dependent Variables or Outcome Measures

Our primary outcome will be live birth rate per embryo transfer. The clinical pregnancy rate as well as the rate of twin gestation and OHSS (ovarian hyper-stimulation syndrome) will be secondary outcomes.

4.3 Risk of Harm

The FDA warns against using Lupron during pregnancy, due to adverse events seen in animal studies. However, these studies used continuous injections of Lupron. Moreover, Lupron use in human pregnancies has never been found to cause harm. The dosage of Lupron that will be given (1 mg) is degraded by 50% in less than 3 hours. This means that after 15 hours (5 half-lives), only about 3% of the original dose (0.03 mg) still exists in your system. Thus, the risk to the baby is minimal, if any, considering the embryo does not even implant into the uterus for three to five days after embryo transfer. Other potential risks are pain, bleeding, or infection at the site of injection.

4.4 Potential for Benefit

Studies in humans have shown that using Lupron increases pregnancy and live birth rates during IVF. The formulation and dose of Lupron used in this study is short acting and is metabolized and excreted from the body before implantation occurs.

5. Data Handling and Statistical Analysis

A computer-generated list of random numbers will be used for randomization. Patients will be randomized at the time of embryo transfer.

All databases will be de-identified. The identification key will be kept in a locked cabinet in the office of Genesis Fertility.

The study will take 2 years for recruitment and treatment, and 1 subsequent year for follow-up data collection (live birth status after treatment) and analysis.

Endpoints were listed above and are the gold standard for IVF experiments.

A univariate chi square analysis will be used to compare the two treatment groups with regard to percent of rate of live births in each group. Logistic regression will be used to compare rates in the treatment groups as a function of live transfer versus frozen embryo to determine any interaction effect due to type of transfer. Logistic regression will also be used to control for the possibility of any differences or confounding factors at baseline. A similar analysis plan will be used for the secondary outcomes.

6. Data and Safety Monitoring

Interim analyses will be performed after each 50 patients enrolled to ensure non-maleficance. Block analysis will ensure there is no bias at these interim analyses. We have a Data Safety and Monitoring Board who will be performing the block analyses.

Analysis will include assessment and statistical comparisons of clinical pregnancy rates, ongoing pregnancy rates, live birth rates, and any other complications, including hospitalizations, infections and miscarriage rate. Any significant difference in these outcomes at an interim analysis will trigger cessation of the study, and a complete report will be provided to the IRB that includes all clinical and research data collected in the study.

7. Reporting Results

7.1 Individual Results

Subjects will be informed of their pregnancy status once the information is available, as is done for all patients. Patients will not be informed, even after the study, to which arm they had been randomized.

7.2 Aggregate Results

Our office website posts updates in “blog” format regarding news at the practice. All information regarding study outcomes can be posted in that forum, and patients/subjects are encouraged to check the website for updates.

7.3 Professional Reporting

All data, whether it shows a positive, negative, or non-significant effect will be submitted for publication in a peer-reviewed journal.

8. Bibliography

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