Investigation on the role of follicular homocysteine in assisted reproduction cycles of polycystic ovary syndrome (PCOS) patients

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Patient information sheet

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Study site: Acibadem Fulya Hospital IVF Center, Hakki Yeten Cad Yesil Cimen Sokak 23, Fulya (Besiktas), Istanbul, Turkey

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Note: This document contains all the information necessary to issue informed consent to participate in the study. Please read the document in its entirety and ask for further clarification on any unclear aspect. If you agree, please provide a copy of this document to your family doctor along with the enrolling Physician's contact details.

Ethical aspects

- This study obtained the positive opinion of the local Ethics Committee (Acibadem University Research Ethics Committee)
- This study is conducted in compliance with the rules of Good Clinical Practice, the Declaration of Helsinki and all current legislation

Terms of joining the study

- Participation in the study is voluntary and based on full information of the patient on all its aspects. The patient remains free to refuse participation. Once consent has been obtained, the patient has the option of: A) withdrawing from the study at any time without any penalty or loss of benefits to which the subject is in any case entitled, and B) requesting the destruction of all previously identifiable biological samples stored for to avoid future analyses.
- The study provides for the random assignment of the participants to two possible groups, one subjected to nutritional supplementation, one subjected only to the surveys. Consent to participate is provided before knowing whether you will be assigned to the active intervention or control group.
- The Promoter of the study declares that, in the event of withdrawal of informed consent by the subject, no new information will be collected and added to existing data or databases, except for the right to use the data collected before the withdrawal of informed consent.
- The patient has the right to be informed about any program of new analyses on samples already taken and coded, not envisaged at the time the subject consented to participate in the study. Should this need arise, the investigator undertakes to request a new consent for the performance of the new analyses, which the subject will in any case have the right to refuse.
- Participation in the study is free of charge for the patient.
- The patient has the right to be informed about the results of the study. The investigator will provide this information, when available, only upon specific request from the patient.

Description of the study

Study design

The study involves the recruitment of women over the age of 18 referred to medical care because of infertility and addressed to assisted reproduction and carrying Poly Cystic Ovary Syndrome (PCOS). Assisted reproduction, to which you were addressed for reasons not connected to the present study, involves the administration of hormones to induce the development of multiple follicles in the ovary followed by recovery of the produced oocytes by means of needle aspiration. Thereafter, the oocytes are fertilized in vitro with the sperm of the partner and the resulting embryos are cultivated in vitro until they are ready to be transferred in the uterus, in the hope they implant and start a pregnancy.

The patients having the above characteristics and who have given their consent to participate will undergo an additional test on their follicular fluid at time of collecting the oocytes from the ovaries. This test, which is the concentration of homocysteine, will be executed on the follicular fluid extracted together with the oocyte and will not cause any added procedure that was not already necessary for the standard clinical practice in your case. You are just allowing us to make an additional test and to use the data collected as such.

All the patients releasing this consent will be casually divided (randomisation) between two possible groups: a group destined for active intervention, i.e. women who will take a nutritional supplement; a group intended for non-intervention, i.e. women who will not take the nutritional supplement but who will otherwise follow the same diagnostic and clinical pathway.

At the end of the treatment, the results obtained in the group of women subjected to the intervention will be compared with those obtained in the women who did not undergo the intervention to verify whether the intervention produced any advantages, and which ones.

Study size and duration

The study foresees the recruitment of a total number of 48 women of which 24 will undergo the nutritional intervention and 24 will serve as controls. The patients randomized for the active treatment will assume the test supplement during 2 months before the hormonal stimulation and thereafter during the stimulation. Therefore, the period of direct involvement of each participant, is 3 months. The patients accepting to participate will remain free to withdraw their consent at any time.

Description of the nutritional intervention

If randomly assigned to the active intervention group, you will be asked to take a nutritional supplement called Impryl at the dose of one tablet per day to be swallowed with water. The supplement will have to be taken during 2 months and thereafter during the hormonal stimulation, i.e. until the oocytes produced will be collected, which takes about 10 days.

Impryl is a nutritional supplement already approved and marketed in Turkey and produced in Italy in compliance with Good Manufacturing Practices (GMP) standards.

Impryl should be taken at a dose of one tablet a day, to be swallowed with water, if possible away from meals, for a period of 3 months. It contains, together with the appropriate excipients, a series of micronutrients which are already part of a complete and balanced diet and which are particularly characteristic of a "Mediterranean" type diet (vegetables, cereals, fish). These micronutrients are supplied in the standard daily quantities indicated by the European Food Safety Agency (EFSA) in order to be sure that the relative requirement is met regardless of the diet one is taking.

Impryl does not carry particular intake warnings other than the prohibition of administration to children under 3 years of age, to not exceed the recommended dose and to not use the supplement as a replacement for a healthy and balanced diet.

No adverse events are described or expected. However, it is a legal obligation and good clinical practice to note and record any symptoms or negative conditions potentially caused by the intake. In the event of serious or urgent symptoms, the patient may contact the investigator and/or the treating physician.

Impryl's nutritional content is listed below.

Ingredients	Per day (1 tab)	% NRV
Betaine	200 mg	
L-cystine	200 mg	
Niacine	16 mg	100%
Zinc	10 mg	100%
Vitamin B6	1.4 mg	100%
Riboflavin (Vit. B2)	1.4 mg	100%
Methyl folate	400 μg	200%
Vitamin B12 (methylcobalamin)	2.5 μg	100%

NRV: nutrient reference value as per Reg. (EU) n.1169/2011

Purpose of the study and possible benefits

The study aims to demonstrate that the amount of homocysteine contained in the follicular fluid may serve as an indicator of the quality of the oocyte contained in the same follicle and of the reproductive potential of the embryo generated from the same oocyte, i.e. that a lower homocysteine content marks a better outcome. If confirmed, this could allow a better selection of the oocytes to be used for in vitro culture aiming to improve the efficacy of the treatment in future patients.

A second aim of the study is to test the possibility that the assumption of a combination of micronutrients, which were already shown to be effective in reducing blood homocysteine in PCOS patients, is able to reduce homocysteine also in the follicular fluid of PCOS ladies.

The specific advantage for the patients randomized for the active treatment is that they will be entitled to assume a treatment that has a true potential to improve their clinical outcomes and to do so under strict medical control. The patients randomized to the control group will not enjoy the above benefit, however they will contribute in the validation of a diagnostic procedure and, possibly, of an effective intervention that could turn useful also to them in case of future fertility treatments.

On the other hand, the risks associated with participation are extremely limited if not absent. There is no addition of invasive diagnostic practices (only an added analysis on the follicular fluid that would have been taken in any case) and, for the patients who will take the supplement, there are no known or presumed risks associated with this intake (natural micronutrients, certified production).

Concomitant treatments

The study foresees that the enrolled patients are not being treated with oral antidiabetic drugs, insulin, antihypertensive drugs or hormones of any kind. Since you have been offered participation in the study, the enrolling doctor has already verified that you are not following any of these treatments. If during the study you should need to take a type of drug among those listed above,

please inform the investigator doctor who will exclude you from the study starting from that moment.

The study also assumes that you did not take nutritional supplements in the week prior to enrolment, which has already been verified, and then for the entire duration of your participation in the study (3 months following). If during the study you should need to take other nutritional supplements other than the one being studied, please inform the investigator doctor who will exclude you from the study starting from that moment. This restriction also applies to patients assigned to the control group.

Concomitant pathologies

The study expects that the enrolled patients are not affected by systemic or endocrine diseases including hypertension and thyroid disease. If a new pathology is diagnosed during the study, please inform the investigator doctor who will assess the nature of this pathology and its possible incompatibility with the study and, in this case, exclude you from the study starting from that moment.

Privacy protection

Your personal and health data will be accessible only to the Investigating Doctor and the health personnel of the facility as normally happens and will be protected in compliance with the laws in force as per common practice without any modification induced by participation in the study.

In fact, all your data relating to the study will be collected and managed in an absolutely anonymous form. The only study document on which your identity will appear will be the randomization list, i.e. the list used to randomly assign the treatment group: on this list, the enrolling doctor will write down your personal details next to the assigned position and will keep this list privately.