

3. To avoid an overdosage, only that dosage of the stimulating agent which ensures the continued growth and development of the primary cohort of follicles should be administered.

4. Caution should be exercised with endogenous LH increases. It is best to cancel treatments when an LH surge occurs before the usual ovulation time of the patient and when the dominating follicle(s) have not reached the size of 21 mm or more.

5. The treatment should be cancelled when progesterone rises without an LH surge and the follicle number is low (below 6).

6. In any cycle in which an LH surge occurs in the presence of more than 5 follicles the treatment should also be cancelled.

7. HCG should be administered when the dominating follicle is 21 mm or larger before progesterone has increased significantly.

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0014-4754/85/121502-06\$1.50 + 0.20/0

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Extracorporeal fertilization of human oocytes and their replacement; suggested simplifications

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Key words. In vitro fertilization; oocyte replacement.

Introduction

Extracorporeal fertilization of human oocytes and intrauterine replacement are now accepted techniques which are offered to infertile couples all over the world². The new techniques may well within a decade more or less totally replace surgery of the fallopian tubes and also be an attractive new technique to overcome certain male infertility factors⁶. For the time being, though, they are mastered by only few centers and this is surprising, taking into consideration the apparent simplicity of the techniques. In the following we would like to stress certain

simplifications which can be applied without decreasing the 'success rates' in the various parts of the technique. In the following a brief inventory of the various steps of a procedure is made, finishing with a list of suggested simplifications for the in vitro fertilization-embryo transfer (IVF/ET) technique.

Natural or hormone stimulated cycles

During the last years most groups working in this field of research have tended to abandon the natural cycle in favor of stimulated cycles⁷. Clomiphene alone in oral

doses of 100–200 mg daily for five days or clomiphene followed by daily injections for 2–4 days of human menopausal gonadotropin (HMG), 150 IU per day, has been suggested for induction of mild superstimulation of the ovaries⁸. In order to induce a more marked superstimulation Jones et al.⁴ have described a schedule for continuous treatment with HMG from day 2–3 in the cycle for 5–8 days. Also other forms of stimulation involving e.g. Tamoxiphene or Stimovul® (Organon) have been suggested. There seems to be no doubt that clomiphene alone is most easy to handle from the patient's point of view and also generally gives a more predictable time for ovulation than other schedules. The initial hormone treatment can principally be followed by administration of exogenous HCG or by a natural endogenous LH peak. The prediction of the optimal time for oocyte collection is easier when HCG is used, although the new techniques for urinary LH determinations are not too laborious. Of importance in this connection is the statement by Edwards at an international meeting in Vienna in June 1983, that their success rate is approximately 50% higher when clomiphene is combined with an endogenous LH surge compared to clomiphene/HCG treatment.

Hormone analyses and/or ultrasound for monitoring of follicular development

During one year in our laboratory repeated sonographic examinations were used as the only method for predicting the optimal time for HCG administration and retrieval of oocytes⁹. 80% of the recovered oocytes fertilized and cleaved in an apparently normal way beyond the 2-cell stage at the time for replacement (48–53 h after insemination). The mean diameter of a dominant follicle at the time for the HCG injection was 19–20 mm (two dimensions). In 42 of these patients blood samples were drawn at the time for HCG injection and analyzed for E_2 in retrospect (mean E_2 value 3.570 pmoles/l). In this group three patients became pregnant. However, the E_2 levels in stimulated cycles reflect the total steroid production of all larger follicles. Consequently, the total follicular volume of follicles (exceeding a diameter of 10 mm) as measured by ultrasound is better correlated to the E_2 levels than to the mean diameter of a dominant follicle. In conclusion, it does not seem obligatory to have access to a laboratory for acute steroid analyses.

Aspiration techniques

The different techniques for oocyte recovery are listed in the table.

Operation	Anesthesia	Limitations
Laparoscopy	General	Severe adhesions
Ultrasound guided aspirations ¹⁰		
a) Transvesical	General or local	–
b) Transvaginal	Local	–

It is well known that severe adhesions can limit the accessibility to the ovary. In the use of ultrasound guided aspirations periovarian adhesions are generally an ad-

vantage rather than a disadvantage, since they help to fixate the ovary. Transvesical puncture under local anesthesia may cause pain especially when passing the needle through the posterior wall of the bladder. This is of special significance if many follicles are to be punctured. Transvaginal aspirations are readily performed under local anesthesia, although the position of the ovaries may sometimes not favor this route for puncturing.

Replacement of ova

Immediate replacement of nonfertilized oocytes in the uterine cavity together with spermatozoa has resulted in pregnancies, although only in occasional cases⁵. Fertilization during short-time incubation in vitro for 5–8 h prior to replacement has, according to Craft¹, been discouraging. Feichtinger and Kemeter recently reported a relatively high pregnancy rate when replacements were performed at the pronuclear stage approximately 24 h following insemination³. The highest pregnancy rate is, however, still reported when the in vitro culture is prolonged up to 40–55 h following insemination¹². The composition of the medium may well be a factor that influences the optimal time for culture. However, prolonged culture for 60–70 h does not seem to increase the success rate and should therefore be avoided.

Patient, position and time in bed following replacement

No significant differences seem to exist between various positions of the patient during replacement. The time in bed following replacement has varied between 1 and 24 h in various successful groups and therefore does not seem to be of crucial importance.

Placental biopsies or amniocentesis

Obligatory chromosomal analyses of all pregnancies resulting from an IVF/ET procedure was initially recommended. However, since a few of these interventions are likely to have caused abortions of chromosomally normal fetuses, and since more than 200 children without chromosomal abnormalities have already been born, it might be suggested that 'normal' criteria for chromosomal analyses (age, risk factors) should be applied on this group of patients¹¹.

Suggested simplifications of the various steps of the IVF/ET procedure are:

- 1) Simple written information about the principles and the practical procedure.
- 2) Stimulated cycles in fixed schedules.
- 3) Repeated hormone analyses in serum or urine might be replaced by repeated ultrasound examination.
- 4) Ultrasound guided follicle aspiration under local (or light general) anesthesia (out-patient procedure).
- 5) Minimize time between aspiration and replacement.
- 6) Minimize time in bed following replacement.
- 7) Restrict placental biopsies or amniocentesis according to 'normal' criteria.
- 8) Consider pregnancy and delivery as 'normal'.
- 9) Repeat the procedure (with modifications, if necessary) 6–8 times.
- 10) Stop treatment if couples develop psychological problems.

In conclusion, it should be emphasized that simplifications of the technique are only justified if they do not negatively interfere with the success rate which in almost all groups is still unacceptably low, at least when based on total patient numbers. It is, however, our belief that IVF/ET will appear soon as an out-patient procedure in many countries. Three term pregnancies have already been achieved by our own out-patient procedure according to the outlined simplifications.

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0014-4754/85/121507-03\$1.50 + 0.20/0

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Multiple pregnancies in gonadotropin-stimulated cycles after human in vitro fertilization (IVF) and embryo replacement

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Key words. In vitro fertilization; embryo replacement; multiple pregnancies; sterility treatment; follicular puncture.

Introduction

The fertilization process, which till recently took place in the obscurity of the mother's womb in mammals, including the human and other primates, can be performed nowadays extracorporally. The current developments have dramatically testified that external fertilization, a phenomenon well known in fish, can now be regarded as a routinely applicable method of assisted fertilization in man. After various indications oocytes are aspirated from the follicles, inseminated in vitro with husband's sperm and replaced into the mother's womb after reaching a normal-looking four-cell stage. Various methods of preparing the patients for this technique have been applied^{6,10,11}. It is the aim of the present paper to report on a large number of follicular punctures, in vitro fertilizations and embryo replacements in gonadotropin stimulated cycles. Multiple pregnancies occurred in 50% of the pregnancies. Is this a desirable or a necessary side effect of this technique of sterility treatment?

Material and methods

1) Hormonal preparation

In order to achieve a higher frequency of aspirated oocytes per cycle, we have been stimulating our patients, since September 1982, with Clomid/hMG/hCG, Clomid/hCG or hMG/hCG alone. It is known that in the natural cycle hMG suppresses an endogenous LH rise. If a spontaneous LH surge did not occur human chorionic gonadotropin (hCG) was used and pelviscopy for follicular aspiration was scheduled 36 to 38 h after the administration of 10,000 IU hCG. hMG was given individually according to the daily measured estradiol response and follicle sizes measured by ultrasound scans. Some patients were stimulated with 150 mg Clomid from day 3 to 7, some from day 4 to 8 or from day 5 to 9 depending on the length of the previous cycles, recorded by the patient herself. The development of an estradiol plateau following a continuous increase in correspondence to the num-