



FULFILLING WOMEN'S REPRODUCTIVE INTENTIONS

Cost-effective approaches to in vitro fertilization: Means to improve access

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Abstract Many childless couples would like to have access to in vitro fertilization (IVF) through public-sector programs, but such programs are scant because of the high costs that IVF entails today. A solution for health departments worldwide might be to leave IVF methods requiring expensive equipment and ovarian stimulating hormones – such as human recombinant gonadotropins, plus gonadotropin-releasing hormone analogues to prevent a surge of luteinizing hormone – to the private sector. Rather, health departments could focus on methods using less equipment and no ovarian stimulating agent at all if possible. If not possible, inexpensive clomiphene citrate could be used, combined with human menopausal gonadotropin if needed. Before embryo transfer, oocyte maturation could occur in vitro or in a makeshift incubator: a tube closed, wrapped, and left in the woman's vagina for 24 h. To prevent short- and long-term costs as well as possible lifelong problems, the transfer of multiple embryos should not be performed.

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1. Background

Infertility is a common problem all over the world. Although the desire to have children can be heightened by the social and psychological environment, especially in areas where the birth rate is

high, it is probably as biologically grounded in humans as it is in other animal species.

In vitro fertilization (IVF) and methods evolving from IVF have revolutionized the possibility of helping childless couples. It is estimated that more than 2 million children have been born following IVF, but this technique has not been widely used in less affluent areas because of its high cost. Even rich countries are limiting access to IVF because of cost. In most countries, the public sector offers only a limited number of IVF cycles. For instance, in Stockholm, Sweden, the County Council only offers

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2 treatment cycles. A low-cost model would be welcome, and one has proved to be as effective as down-regulated cycles for women older than 40 years in Austria [1].

2. What is the cost of IVF?

2.1. Salaries

In affluent countries, the salaries of trained staff account for the greatest part of the cost. Both absolutely and relatively, this cost would be much lower in developing countries where salaries are lower. Yet a problem could quickly arise: once trained in providing IVF, public sector personnel from less affluent countries might launch private clinics to secure higher income for themselves, thus depriving most childless persons of IVF access. Retaining trained staff in the public sector is a challenge at a time when access to IVF needs to be facilitated.

2.2. Ovarian hyperstimulation

The hormones used to obtain more mature oocytes, and hence improve the likelihood of pregnancy, are another important cost factor. Human recombinant gonadotropins and gonadotropin-releasing hormone (GnRH) analogues account for at least 50% of IVF costs. Even though acceptable pregnancy rates are achieved using either clomiphene citrate (CC), or a combination of CC and human menopausal gonadotropin (hMG), or hMG only [2–8], higher rates are achieved using recombinant gonadotropins with GnRH analogues – the latter to prevent a surge of luteinizing hormone (LH). More oocytes are obtained with recombinant gonadotropins and GnRH analogues, with a lower cancellation rate, and the pregnancy rate is therefore higher. In areas where the cost of hormone treatment is the factor that places IVF out of the reach of those who need it, a less effective treatment would be better than no treatment at all.

2.3. Equipment

Neither the cost of ultrasonographic equipment suitable for monitoring ovarian follicular development and retrieving oocytes, (about € 5000), nor the cost of aspiration needles and embryo transfer catheters (about € 15 per treatment cycle) can be avoided.

The IVF laboratory studies, where cleanliness is a cost in itself, are also expensive. Even the most low-cost IVF program will need an autoclave, clean

water, ethanol, and disposable material such as culture tubes or dishes, as well as needles and pipettes to handle the gametes, although autoclaving multi-use pipettes can be considered. Incubators are expensive, and their optimal use needs to be identified. A laminar flow hood is helpful, and probably not too costly. A stereo microscope is definitely needed. Culture medium, which has to be of good quality, is also a large cost.

3. Low-cost hormonal stimulation

3.1. No hormonal stimulation

Not to use hormonal stimulation at all would, of course, be the most economical means of achieving IVF. Rates of confirmed pregnancies with natural-cycle IVF have been reported to be between 7.5% and 19% per cycle [9–12]. A very low-cost model using natural-cycle IVF and vaginal culture (described below) resulted in a pregnancy rate of 10% per cycle [13]. Natural-cycle IVF combined with pronuclear-stage transfer would be affordable almost anywhere. Repeated cycles would be needed, but the cost would be low even if every woman needed several attempts.

3.2. Maturation of oocytes in vitro (IVM)

This is an alternative when no hormonal stimulation is needed in the woman and several oocytes can be obtained per treatment cycle. The laboratory part, however, is more demanding than when using mature oocytes after hormonal stimulation. And although the pregnancy rates have not been as high as those in stimulated cycles [14–18], IVM has been particularly satisfactory for women with polycystic ovaries, who achieved similar pregnancy rates with IVM and IVF [17]. Intracytoplasmic sperm injection (ICSI) was thought to be required, but it was recently shown that this was not the case, as in one study the implantation rate was higher using IVF (24.2%) than ICSI (14.8%) [19]. The pregnancy rate recently achieved at this clinic in Helsinki, in the era of GnRH analogues, is similar to the rate it previously obtained using conventional IVF. Adding only human chorionic gonadotropin (hCG) before aspiration of immature oocytes has helped increase the number of oocytes aspirated [20,21]. Thus, IVM is an option to be considered, at least after further improvement. The laboratory work is, however, more demanding than during stimulated cycles.

Optimal inclusion criteria for an IVM program could be regular menstrual cycles in a woman

younger than 36 years; at least 5 small follicles in both ovaries seen ultrasonographically at the beginning of the cycle; and at least 0.5 million/mL of motile sperm after simple swim-up. Oocyte retrieval can be performed on days 9 through 13, when the thickness of the endometrium is at least 5 mm, preferably 7 mm [18]. A dominant follicle does not influence the outcome [16]. As much as 5000 IU of hCG can be given 36 h before retrieval [22]. After 28 h in the maturation medium (TC199 supplemented with the patient's serum [10% of TC199 volume]; 0.3 mmol/L of pyruvate; and 0.5 IU/mL of hMG), the oocytes are ready to be inseminated with spermatozoa in a dish. Embryo transfer is carried out the next day. Two-pronuclear-stage embryos are selected for transfer. If there are other zygotes, they may be cryopreserved using vitrification [23,24] if liquid nitrogen is available.

3.3. Clomiphene citrate, combined with hMG if needed

Clomiphene citrate has proved to be safe in ovarian stimulation, and the tablets are not expensive. It was used alone in early IVF stimulations [2], and then extensively in combination with hMG. In terms of costs, CC alone is a better option, but using hMG a couple of times is not excessively costly. Luteal-phase support is not needed, and CC is administered orally, 100–150 mg daily on cycle days 3 to 7. If good follicle development is not achieved using CC alone, 150 IU of hMG can be injected subcutaneously on days 8 and 10 of the cycle. When the largest follicles are about 18 mm in diameter, on days 11 or 12, 5000 IU of hCG are injected subcutaneously. The oocytes are aspirated 32 h later and inseminated on the same day, and the transfer of pronuclear-stage embryos is carried out the next day. The problem with this program, which was widely used in the 1980s, is the possibility of premature LH surges. Such surges can be prevented using a GnRH antagonist, but at high cost. Even monitoring women for LH surges using urine LH kits may be too expensive. In the case of an early LH surge the woman will ovulate, or the oocytes will not be fertilized – which may be considered acceptable for some cycles in this low-cost model. The cause of nonfertilization will remain unknown in these cases.

4. Laboratory studies in the low-cost IVF model

Quality laboratory work is of the utmost importance for successful IVF. A self-sterilizing incubator

would, of course, provide the best results. Hospitals that have steady access to electricity may find it worthwhile to acquire such incubators, with a device to monitor gas flow. Such a system costs some € 6000, but a very simple system would also work. In the early days of IVF, some teams placed closed, tightly wrapped culture tubes in the woman's vagina [25,26], and pregnancies occurred. This option may be acceptable for 1-day cultures up to the pronuclear stage. Other types of inexpensive incubators are also available, as described below.

Cleanliness is an important factor for successful IVF. Whatever the method used, laboratory surfaces must be cleaned with ethanol. Used as fuel for cars, ethanol is inexpensive and widely available; however, it requires a well-planned delivery system and its use must be controlled. A laminar flow hood is helpful in maintaining conditions of cleanliness suitable for in vitro work, and investing in one should be considered.

Quality-controlled culture media are expensive, but a ready-made controlled medium is by far the safest for successful IVF and even the most expensive ones are cost-effective. KSOM, mixed with the woman's serum would be options. Self-made media are less costly, but they require very careful laboratory assessment.

5. A slimmed-down version of IVF with vaginal culture

A very slimmed-down version of IVF with vaginal culture [25,26] may be a way to avoid purchasing an incubator. After CC stimulation or during a natural cycle, the oocytes are collected when the largest follicles are about 18 mm in diameter and placed, together with spermatozoa prepared by swim-up, in a tube containing a commercial culture medium. The tube is then closed, wrapped, and placed into the vagina with the recommendation to push it back immediately if it threatens to fall out. After 24 h, the oocytes/zygotes are taken out of the tube and observed on a stereo microscope. Zygotes with 2 pronuclei are placed in fresh medium, and 2 of these are transferred to the woman.

6. Single-embryo transfer prevents the costs of a multiple pregnancy

In several European countries, e.g., Finland, Sweden, and Belgium, single-embryo transfer (SET) has become the norm in recent years [27–31]. In

Sweden, pregnancy rates have remained the same even though 70% of embryo transfers are now SET [31]. It is easier to perform embryo selection at the cleavage stage than at the pronuclear stage. Hence, the pregnancy results after pronuclear-stage transfers are not expected to be quite as good as they are after cleavage-stage transfer. But it is also possible to select embryos at that stage. The morphology of the nucleoli, the developmental rate, and the morphology of the original oocyte are factors to take into consideration.

Multiple pregnancies, and premature births as a consequence, are very costly for both health care systems and families. The costs of neurological disorders following a premature birth are compounded throughout the life of those affected, and such disorders may be devastating in many ways for the family.

Hence, multiple pregnancies should not be deliberately induced as a way to save resources, and SET should be the norm for at least the first 2 treatment attempts. Later on, maybe 2 embryos could be transferred at a time, but never more than 2. Thus, a functioning cryopreservation system for pronuclear-stage embryos ought to be available.

7. Freezing of pronuclear-stage zygotes by vitrification

If liquid nitrogen is available, the rest of the 2-pronuclear zygotes are transferred to a vitrification medium [23,24] and, as fast as possible, placed into a liquid medium using pipette tips or thin straws – which are then closed to become tubes – and preserved in a nitrogen container. Following vitrification, pronuclear zygotes have a 70% survival rate after thawing.

8. Efficacy testing and staff training

Before these slimmed-down versions can be implemented, their efficacy must be assessed at a unit with extensive experience of IVF treatment, and staff must be trained at the same unit. The International Federation of Fertility Societies working group has planned these activities in several locations.

We are beginning to test the efficacy of these models at the Huddinge Fertility unit of the Karolinska University Hospital, in Stockholm, Sweden. But many more units are needed for training, and help is required to establish such units.

9. Making cost-effective IVF work in governmental hospitals, and getting trained staff to stay

When data on the outcome of pilot studies on low-cost IVF become available, it should be possible to carry out a preliminary cost–benefit analysis. It should also be possible to assess the proportion of women, according to the etiology of their infertility, who would benefit from this approach, and hence the cost of launching such a program.

These data could be organized in a monograph to be presented to the health departments of low-resource countries. Such a monograph would emphasize sociological arguments for dealing with the traumatic condition of childless couples and provide a description of the likely demand for IVF services. The scenario for equipping a laboratory, training staff, establishing and maintaining links with a parent laboratory, and delivering the needed clinical services would be detailed. The monograph would describe the advantages of embedding IVF services in a national health system, and could be used as a basis for seeking external funding.

The results obtained with the low-cost methods described in the present article probably will not be as good as those obtained with the more expensive methods. These less satisfactory results would act as a disincentive for using low-cost methods in private-sector clinics. Moreover, as staff would require retraining in a more drug-oriented environment with a greater variety of clinical conditions, they would be less likely to be led away from the public sector. These considerations would apply to a lesser degree to laboratory and nursing personnel, but the use of more complex incubation systems would require specific skills that such personnel would not readily have.

Private clinics might choose to offer low-cost IVF treatment to less affluent couples, and a measure of competition could be healthy. Private clinics are usually located in large cities, where affluent groups reside. These clinics are not likely to administer low-cost treatment to their affluent patients at premium prices, with a poorer pregnancy rate than their private-sector competition. Private clinics certainly may decide to run satellite units offering low-cost IVF in rural areas in conjunction with a central, city-based unit. However, such a large population is likely to request low-cost IVF that the viability of government-run units would not be threatened.

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