The Patient-Friendly IVF Cycle

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Abstract

Background: In vitro fertilization (IVF) is an involved fertility treatment, which incorporates multiple steps including injections, blood and ultrasound testing, surgery, and anesthesia. Despite recent improvements in success, IVF remains underused because of its expense and inconvenience. The purpose of this report is to review various protocols that reduce expense and increase patient acceptance of IVF.

Materials and Methods: Boston IVF is the most experienced IVF center in the United States. Over the last 15 years, it has developed streamlined clinical protocols to help make IVF more acceptable and convenient for patients. Many of these procedures are reviewed in this report.

Results: Methods to improve patient education are reviewed. Simplified methods to administer medications and monitor response are examined. Less restrictive instructions following the embryo transfer, among other considerations, can make IVF better tolerated.

Conclusions: IVF need not be overcomplicated and burdensome for couples. We encourage IVF centers to review their current practices and evaluate methods to maintain the highest quality and keep IVF as simple as possible. By doing so, IVF costs will be contained, and the large number of women who currently do not seek care will be reduced.

Since its introduction 20 years ago, in vitro fertilization (IVF) has become a commonly performed infertility treatment. IVF clinics are found in almost every country worldwide, and IVF is used to treat most causes of infertility, including male factor, endometriosis, tubal disease, and unexplained infertility. Despite the proven success and benefits, IVF is unavailable to many patients. The associated costs and the effort needed for patients to undergo IVF treatment have both contributed to decreased access.

Cost is a major obstacle for most patients. Treatment involves injections of expensive medications; monitoring ovarian response to medication with serum blood tests such as estradiol (E_2), luteinizing hormone (LH), and progesterone (P_4); monitoring follicle development with pelvic ultrasound examinations; egg retrieval; fertilization of eggs and then embryo culture; and, finally, embryo transfer. If any embryos remain after transfer is completed, there can be an additional cost for freezing and storing the spare embryos.

IVF is also physically and emotionally intense.[1–3] Patients must learn an extraordinary amount of information to adequately prepare for IVF treatment. They must learn how to mix and administer injectable medications, interrupt their daily routines for serial blood tests and ultrasound examinations, and undergo a brief surgical procedure to retrieve oocytes. The financial and emotional costs may dissuade couples from pursuing the currently most successful treatment in the therapeutic arsenal.

At Boston IVF, it was postulated that if IVF were easier to undergo, it would be appealing to more couples. Therefore, services were streamlined to develop the "patient-friendly" IVF cycle. Several other forces also motivated this streamlining. Massachusetts has a legal mandate requiring those insurance companies based in the state to offer fertility services. Reimbursement is a fixed dollar amount that incorporates all fees for procedures during treatment excluding medications. Patients are not billed directly for any individual services; rather, the practice receives a global fee that encompasses all aspects of IVF treatment including the costs of all blood tests, ultrasound examinations, anesthesia, operating room time, surgeons' fees for egg retrieval and embryo transfer, laboratory fees, and pregnancy tests to discover if the treatment succeeded.

This report reviews the protocols developed at Boston IVF, which is the largest provider of IVF services in the United States. The patient-friendly IVF cycle developed at Boston IVF has led to greater patient acceptance and reduced costs.

Patient Education

Patients undertaking IVF must master a lot of new information. They need to know about the steps in the process and they must learn how to administer medications. This has been traditionally accomplished by an approximately 1-hour meeting with a nurse and often occurs in classes with more than one couple. This is costly in terms of office staff time. Furthermore, rote repetition of the same subject matter is not gratifying for the instructors and can lead to unintentional variation in content over time.

To provide consistency in the IVF orientations and reduce the time that a nurse must provide rote teaching, an interactive multimedia education system called HealthBank™ has been used. Developed by RSVP Information Systems Inc. (Lexington, MA), the system is a programmable series of interactive 2- to 3-minute video clips. An IVF orientation ordinarily employs 10 to 12 video clips and lasts about 25 to 30 minutes. The

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specific sequence of video segments used is programmed for each couple in advance, and the content can be tailored to meet their specific needs. For example, a couple who will have ICSI used in their cycle will have a video clip about ICSI in their orientation, whereas a couple undergoing conventional IVF will not. To make the multimedia presentation more personal, each physician recorded an introductory video clip, and each orientation begins with the clip of the patient's own physician.

The multimedia presentation teaches patients about all of the steps of IVF, including injections. The interactive video touch screen allows patients to repeat any segment that they wish to review, thus allowing for repetition and reinforcement that is not possible in a meeting with multiple couples. After the presentation, the couple meets with a nurse, who provides an injection lesson if necessary and reviews the specific treatment protocol prescribed by the patient's doctor. The HealthBank system saves at least 30 minutes of a nurse's time per couple.

Patient Access

Easier access makes patients more likely to seek and more comfortable during treatment. Most patients prefer to be seen close to home or work; therefore, community-based satellite offices tend to be well received. At satellite offices, patients can be seen for consultations and undergo IVF cycle monitoring, including blood tests and ultrasound examinations. The highest cost in setting up an IVF program is construction and maintenance of the operating suite and laboratory.[4] The experience at Boston IVF is that patients are happy to have egg retrieval and embryo transfer performed at a high-capacity central IVF facility when they have access to community-based satellite offices for consultations and cycle monitoring. The centralization of costly services and the decentralization of community-based care is both cost effective and patient friendly.

Ovarian Stimulation

An onerous task that patients face when pursuing in vitro fertilization is learning to perform intramuscular (IM) injections. Although IM injections can be self-administered, it is common for a patient to conscript her partner. This can lead to logistical difficulties if the partner becomes unavailable due to unforeseen circumstances in the middle of a treatment cycle. Enormous stress is induced when a patient is forced to find another trained and willing individual to inject her medications. In contrast, subcutaneous (SC) injections are routinely self-administered; for example, diabetics administer insulin to themselves many times daily by SC injection. SC injections are also better tolerated generally than IM injections. To make self-administration of injectable medications as easy as possible, IM injections have been abandoned at Boston IVF. Only SC injection is taught to patients during the instruction phase of IVF orientation. Therefore, all injectable medications prescribed during treatment are administered subcutaneously by the patient herself.

Most patients at Boston IVF use gonadotropin-releasing hormone agonist (GnRH-a) in addition to follicle-stimulating hormone (FSH) for controlled ovarian hyperstimulation. In the past, this required one SC injection of GnRH-a in the morning and one SC injection of FSH in the evening. However, some patients are receiving a treatment regimen that requires both morning and evening doses of both GnRH-a and FSH. When a preliminary evaluation demonstrated no adverse interaction of these two water-soluble products, a single combined injection of GnRH-a and FSH was substituted. Patients prepare the vial of FSH and leuprolide acetate separately, inject the GnRH-a medication into the prepared vial of FSH, and then administer the combined solution. Reducing the number of daily injections from four to two or from two to one was found to reduce injection-related anxiety of even the least "needle-phobic" patients. In the year since the change was made universal, no adverse consequences have been seen from the combined injection.

Human chorionic gonadotropin (hCG) is labeled for IM injection; however, data show that SC administration of hCG is equally effective as IM.[5,6] Since 1998, Boston IVF has administered hCG (10,000 IU) via SC injection to induce oocyte maturation before IVF. No clinical differences have been noted in the number of eggs retrieved and fertilized or the quality of embryos and pregnancy rates, although local reactions (stinging and redness) are somewhat more common with SC compared to IM injection.

Monitoring

A long suppression protocol, in which GnRH-a is administered beginning on cycle day 21, is used for most patients. While the patient is receiving GnRH-a, menstruation is awaited before FSH is administered. On average, the interval between the start of GnRH-a treatment and the onset of menses is 7 to 10 days. The onset of menses has been found to be an excellent marker of pituitary/ovarian suppression. Therefore, baseline ultrasound or blood tests routinely are not obtained prior to FSH treatment. Baseline studies are ordered when the cycle immediately preceding the start of GnRH-a treatment included ovarian stimulation or when menses does not occur within 14 days of starting GnRH-a treatment.

Once menstruation occurs while receiving GnRH-a treatment, FSH treatment begins, continuing for 5 days prior to the first ultrasound and estradiol measurement. Therefore, the first monitoring session during the patient's IVF cycle generally occurs 12 to 21 days after she began taking GnRH-a. In some programs, a patient might have to endure hormonal testing or ultrasound monitoring three to five times. At Boston IVF, the patient's prior response to gonadotropin therapy is used as a gauge for her IVF cycle dosages. Following the patient's first monitoring, her initial response to medications is looked at and her anticipated response is projected using her past performance and the current cycle indices. To avoid disruption of the patient's work and home life, she is asked to return for monitoring only when necessary; it is not uncommon for 3 or more days to pass between tests. On average, three ultrasound tests are obtained per cycle.

The objective is to obtain as many follicles between 15 mm to 20 mm without exceeding an E_2 level of 3600 pg/mL. To

further reduce the number of blood tests and ultrasound examinations, patients are often "pre-triggered" with hCG. If the estradiol level is less than 1800 pg/mL, and follicular size indicates that one additional day of stimulation is warranted, then the patient is asked to take GnRH-a and FSH that day and administer hCG the next day. This cuts out one additional ultrasound examination and blood test, hence the term "pre-trigger."

Measurement of LH and P_4 levels is not routinely performed with E_2 but is requested for all patients receiving microdose GnRH-a since these individuals are slightly more likely to have a premature LH surge. In addition, E_2 is not measured on the day after hCG administration, since this information does not appear to predict outcome at all.

Oocyte Retrieval

Without medication, oocyte retrieval is uncomfortable. Various ways of inducing analgesia or anesthesia have been described, including general anesthesia,[7] combinations of oral and IM narcotics, paracervical blocks, and even regional anesthesia.[8] Most patients at Boston IVF prefer to be asleep, thereby avoiding all intraoperative pain.

General anesthesia has been found to be safe and effective in oocyte retrieval.[9] An anesthesiologist administers anesthesia for every egg retrieval procedure at Boston IVF, using propafol and fentanyl and adding isoflurane (rarely) when needed.[10] To reduce bleeding and pain, disposable needles are used and multiple vaginal punctures are avoided. Because the patient is completely comfortable, the follicles are not irrigated, and the retrieval needles are perfectly sharp and straight, the average duration of egg retrieval from initial needle puncture until the needle is finally withdrawn averages less than 15 minutes. The short-acting nature of the anesthetic agents used and the lack of neuromuscular blockade allows patients to quickly recover and therefore be discharged 60 minutes after completion of egg retrieval, compared to a reported average of 90 to 120 minutes.[11]

Embryo Transfer

Embryo transfer is performed supine, without stirrups, with the heels widely spaced at the end of the examining table. The patient is not medicated and the use of a tenaculum is avoided if possible. The vagina is cleansed with several sponges soaked with culture media, and then the embryos are transferred. Since all patients at Boston IVF have previously had the cervical canal mapped and the uterine cavity sounded, descriptive notes are present in the chart for the physician performing the embryo transfer.[12] Once the vagina and external cervix have been cleansed, the embryologist loads the catheter and the embryos are transferred using the previously recorded instructions.

A recent report indicated that ultrasound-guided embryo transfer did not improve pregnancy rates with uncomplicated transfers but was worthwhile for patients for whom a difficult transfer was anticipated.[13] If a physician at Boston IVF feels that an embryo transfer might be difficult, the use of ultrasound guidance during the transfer can be ordered. Using ultrasound guidance only when truly warranted reduces the time of the average embryo transfer. Most do not require ultrasound-guided transfer, so the discomfort of the requisite full bladder is also eliminated for the majority of patients.

Post Embryo Transfer

There is more myth in the instructions given to patients after embryo transfer than for perhaps any other aspect of IVF. Some programs require patients to remain at strict bedrest for the nearly 2 weeks from embryo transfer until their pregnancy test. Interestingly, there are no data to support such severe restrictions. In fact, Woolcott and Stanger recently reported that "standing shortly after embryo transfer does not play a significant role in the final position of embryo-associated air bubbles (by ultrasound) and is unlikely to be a factor in determining the position of embryos transferred to the uterine cavity during treatment with IVF."[14] The inclination to restrict patient activity stems from a conception of the embryo being in a delicate state within the uterus. However, this is unsubstantiated by data. In fact, in the active general population, the artificial restriction placed on IVF patients is never practiced.

An analogy can be made between the desire to restrict patients after embryo transfer and the obstetric recommendation of three decades ago. In the 1960s, women were routinely restricted to bedrest for up to 7 days postpartum. This restriction was based on the concept that recovery from the energy expenditure and blood loss of delivery required a period of enforced recuperation. Unfortunately, what was not understood at that time were the implications of venous stasis in women with high estrogen levels, whose clotting factors had been proliferating under the influence of the hormones of pregnancy. An inordinate number of women developed deep vein thromboses and even experienced pulmonary emboli as a result of enforced bedrest. When the restrictions were lifted, these problems disappeared.

Since all recommendations following embryo transfer are based on clinical opinions and are totally speculative, a pathway was chosen at Boston IVF that minimally interferes with patients' day-to-day lives and is patient friendly. Patients walk from the transfer room, get changed, and are then discharged home. Patients receive a loose recommendation to "take it easy" for the remainder of the day of the transfer, but routine activity is not restricted afterwards. Like other centers nationally, pregnancy rates at Boston IVF have continued to climb in light of our unrestrictive policy.

Most IVF centers supplement the luteal phase with progesterone treatment. Progesterone is usually given intramuscularly, which is often painful. To make luteal phase progesterone administration patient-friendly, a polycarbophil vaginal progesterone gel or vaginal suppositories are used instead. A number of studies indicate that vaginal routes of progesterone administration are equivalent to the IM route.[15–18] As expected from previously published reports, no difference in pregnancy outcome between IM and vaginal routes of progesterone administration has been observed.

Some IVF centers measure luteal phase serum progesterone to determine if an adequate amount of supplemental progesterone is being administered, and thus the patient must endure an additional blood draw following her embryo transfer. Measuring serum progesterone is of little benefit in the face of pulsatile endogenous progesterone release, and the validity of a single measurement is dubious. Furthermore, the use of vaginal progesterone is not associated with high serum levels, because of its "first-pass effect," and endometrial responses are related to a local effect rather than serum levels.[19] Therefore, administering progesterone through a vaginal route avoids the discomfort of IM injections, bypasses the need for serum progesterone monitoring, and ensures that the uterus receives the desired amount of progesterone through the first-pass effect.

Conclusions

Pregnancy rates associated with assisted reproductive technologies have improved considerably over the last several years. Improved embryo culture methods, new assisted fertilization techniques, and better ways to perform embryo transfers account for some of the improvement in results. However, the most common reasons for patients to abandon treatment are the stress and inconvenience of the process and the cost.

Sanders and Bruce recently reported on the importance of psychosocial stress in treatment outcome but indicated that the relationships are complex. Converting to a patient-friendly IVF cycle can dramatically reduce both the stress and inconvenience traditionally associated with IVF. The patient-friendly approach also helps to minimize costs. We believe that minimizing both the inconvenience and the cost of the procedure will enable more patients to seek treatment. Furthermore, reduced cost and inconvenience will enable patients to tolerate more IVF cycles and dramatically increase their odds of having a baby.

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