Editorial Article

In vitro fertilization is expensive: when should a couple be advised to stop trying with their own gametes and seek other options? Review of three cases

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Summary

Purpose: To describe refractory infertility cases that preserved many failed in vitro fertilization (IVF) cycles to achieve the goal of delivering a baby. *Methods:* Case reports with a description of the various approaches and change in strategy that finally led to success. *Results:* Factors causing repeated failures in these cases included adverse effects of the controlled ovarian hyperstimulation regimen on the uterine environment, failure to realize that the sperm from a male with a low hypo-osmotic swelling test can cause embryo implantation failure unless intracytoplasmic sperm injection is performed, and the discovery that sperm abnormalities rather than exclusively oocyte problems can lead to embryo fragmentation. *Conclusions:* It is imperative that infertility specialists individualize cases – especially ones that have failed several cycles – and stop using the same process that has repeatedly failed. They should stop and think if there are some less common but important factors they may have overlooked. Merely recommending donor oocytes without exploring other options is inappropriate.

Key words: Refractory infertility; In vitro fertilization; Hypo-osmotic swelling test; Controlled ovarian hyperstimulation; Embryo fragmentation.

Introduction

In vitro fertilization (IVF) is expensive and frequently is not covered by insurance carriers. Even when it is covered there is usually some limit to the number of cycles that are paid for or a certain limit to the amount of money that is given.

There are some patients who are willing to spend huge amounts of money and time to achieve a pregnancy with their own gametes even when the likelihood of success with donor eggs, donor embryos, or even in some instances donor sperm, would be potentially far greater.

We present several cases of couples who persevered many failed cycles to achieve their goal or who were willing to spend money for IVF even though they were advised that the chance of conception with their own gametes was very slight.

Case 1

A 38-year-old woman presented with a 10-year history of infertility [1]. She advised us of her past medical history which was as follows: She had a history of oligomenorrhea and was considered anovulatory with a diagnosis of polycystic ovarian syndrome. She had tubal patency established by hysterosalpingogram and laparoscopy. No endometriosis or adhesions were noted. The semen analysis was normal as were postcoital tests. She failed to conceive despite six years of ovulation induction with clomiphene citrate in a minority of cycles and gonadotropins in the majority of cycles. Egg release was confirmed by sonography in many cycles and the luteal phase was supplemented with extra progesterone taken vaginally. Endometrial biopsies while taking follicle maturing drugs and progesterone supplementation were considered in-phase. Many intrauterine inseminations were performed over the 6-year treatment period but she did not conceive.

At this time the couple decided it was time to try IVF. They flew from the Middle East to the United States to one of the world's leading IVF centers. Unfortunately the woman failed to conceive following two cycles of controlled ovarian hyperstimulation (COH), egg retrieval and fresh embryo transfer. She similarly failed to conceive following two fresh embryo transfers at a world renown IVF center in England. She returned to her middle eastern country where she had IVF-ET performed by a successful IVF center that was willing to grant her request of transferring 12 embryos at a time. Unfortunately she still failed to conceive following six more IVF cycles with 12 fresh embryos transferred each time. Thus she failed to conceive despite 92 fresh embryos being transferred over ten IVF-ET cycles.

Revised manuscript accepted for publication July 26, 2007

Though donor eggs had been suggested, this was not possible for religious reasons. Thus she presented at our IVF center hoping for a different approach. As mentioned she had ten years of primary infertility when she consulted with me. I advised her that sometimes the drugs used for controlled ovarian hyperstimulation (COH) may create an adverse environment that can prevent embryos from implanting [2, 3]. Based on the detection of a protein called progesterone-induced blocking factor (which requires trophoblast invasion for expression) at an earlier time in the luteal phase than normal which has been associated with a very low pregnancy rates, we considered that COH may allow, in some instances, premature trophoblast invasion [4, 5].

Thus our suggestion was to do IVF-ET again but to freeze all embryos at the 2 pronuclear stage and then in a subsequent cycle transfer frozen-thawed embryos. Out of 38 metaphase II oocytes 28 fertilized using conventional insemination and 27 were frozen at the 2 pronuclear stage.

One month was skipped. She was then started on a graduated regimen of oral estradiol followed by progesterone supplementation. Eight embryos were thawed and the best five were transferred (two 7-cell and one 6-cell with ≤ 25% fragmentation and a 5-cell and 2-cell embryo were also transferred). She conceived and successfully delivered a viable full term child [1].

Comment

IVF is expensive and thus many would argue that this woman should have been told to quit. She had had 92 embryos transferred over ten IVF cycles! If she had had three embryos transferred each time, she would have had the equivalent of 31 failed IVF cycles! This couple represents a prime example of people who should be counseled as to when enough is enough and even if donor eggs are not allowed from a religious standpoint, adoption or maybe a donor embryo should be considered.

Nevertheless, the couple's point of view was that doctors are not infallible and maybe another doctor could have a different idea that might lead to success. Indeed, my group has found that the COH regimen itself may cause implantation problems [2-4]. It was surprising that with all the embryos she had made in the past that no one had ever performed frozen embryo transfer. Thus we purposely froze all embryos.

It could be argued that one successful case might have just been fortuitous and that there is no proof that the COH regimen actually caused the problem. The patient was advised that because of the great distance from the Middle East to the United States, that instead of coming here for another frozen embryo transfer right away, when she was ready for a second child, she should ask the doctors to prescribe metformin to see if she could actually be made to ovulate spontaneously. She was also advised that sometimes following a pregnancy women with polycystic ovarian syndrome may spontaneously ovulate for a while. In either case, she was advised to use progesterone supplementation in the luteal phase [5, 6].

She reconsulted us at age 40 to have another frozen embryo transfer. Though she did not take metformin she admitted to having had nine regular menstrual cycles since her delivery but without a pregnancy. However, she forgot to request progesterone support in the luteal phase.

Her consult was calculated to be about three days after ovulation so too late to thaw the embryos and do a frozen embryo transfer since they had been frozen at the 2 pronuclear stage and thus synchronization on a natural cycle could not be achieved. Since she had had intercourse at mid-cycle, she was prescribed 200 mg progesterone vaginal suppositories. She conceived in this natural cycle without embryo transfer and again delivered a full-term healthy baby [7].

This second pregnancy in this same woman provides additional support for the concept that in some women the drugs used to stimulate multiple follicles can have an adverse effect on subsequent implantation [8].

The suggestion had been made to her previously by other physicians to use either donor eggs or a gestational carrier. Since her problem was the COH regimen, both of these options would have worked but would not have provided the ideal objective that she wanted. Furthermore, the expense for a gestational carrier, which would have been the only option based on her religious beliefs, would have been markedly more expensive.

It is not clear why despite all the embryos that were formed from three different IVF centers that no one provided the option of frozen embryo transfer but kept attempting fresh embryo transfer on stimulated cycles.

Case 2

A 34-year-old woman with three years of unexplained infertility and failure to conceive despite eight cycles of COH and intrauterine insemination had failed to conceive following seven cycles of IVF-ET with fresh embryo transfers each time, and in addition four frozen embryo transfers.

She came to us for a second opinion already in the midst of COH for IVF cycle number eight. Her plan was to continue with the IVF center that had performed all of her previous embryo transfers but she would change to our facility for number 9 if she was not successful.

The semen analysis according to the previous IVF center was normal and therefore all oocytes were fertilized by conventional insemination. I suggested that the husband repeat the semen analysis and perform a test not previously performed, i.e., the hypoosmotic swelling (HOS) test.

Though the couple had been advised that the sperm was perfectly normal, especially since they fertilized a high percentage of the oocytes which led to embryos with normal morphology for transfer, I explained that a low HOS test detects an interesting abnormality. In this circumstance, there is normal fertilization but extremely low implantation rates [9, 10].

Though a repeat of standard semen parameters including antisperm antibodies was indeed normal, the HOS test was clearly subnormal with only 42% of sperm showing tail swelling. I advised the couple that this abnormality might be related to the transfer of a toxic factor from the sperm to the zona pellucida by the supernumerary sperm that attach, and that the zona pellucida is incorporated in the embryo membrane [11]. HOS defects are associated with a functional defect in the sperm membrane and the hypothesis is that the toxic factor thus causes a functional defect in the embryo membrane which interferes with its attachment to the endometrium [11].

Therefore, it was suggested that she continue with the IVF center that had performed the previous seven IVF cycles since they started the present COH regimen, but to just advise them to do intracytoplasmic sperm injection (ICSI) since this bypasses exposure of the zona pellucida to the toxic factor. Intracytoplasmic sperm injection seems to fully correct an embryo implantation defect related to the HOS defect [12].

The reproductive endocrinologist initially refused to perform ICSI stating that his beliefs were that the HOS test is a meaningless test. The patient sought my advice and I told her that we would be willing to do her egg retrieval and inseminate the oocytes by the ICSI process. However, I suggested that the couple give the other IVF center one more chance and to inform them that unless they performed ICSI that the IVF would be performed at our center. Reluctantly, the other IVF center agreed to perform ICSI. The woman conceived in that eighth IVF cycle and had a full-term delivery.

Comment

In vitro fertilization is expensive but a donor egg is even more money. Nonetheless even that expense does not compare to the cost of a gestational carrier. The usual assumption by most reproductive centers is that failure to conceive despite transferring normal embryos is either an oocyte problem or a uterine problem.

The mind set of most IVF centers is that the job of the sperm is to fertilize the egg so if normal embryos are formed then the problem is not related to a sperm defect. This is not true as evidenced by implantation defects caused by conventional fertilization with sperm with low HOS test scores as illustrated by this case.

Certainly it is the responsibility of the IVF center to explore possible remediable factors that could explain persistent failure to conceive despite transferring normal embryos. Manuscripts in major reproductive journals have appeared for over 20 years and are still being published about the implantation problems associated with the HOS sperm defect. To be fair to the couple, the aforementioned IVF center should have performed due diligence to determine if they could be missing some key factor to explain the patient's repeated failures.

However, when given the opinion from another IVF center that this could be the reason for the problem, the reproductive endocrinologist did not call me to inquire about the source of my knowledge or the basis of my opinion, or to review recent literature but merely expressed his opinion that he did not believe in the test. He has never published any data refuting the importance of this test. It was not that he was trying something new for cycle 8 but was merely planning to proceed in the same manner that had failed seven times before!

In the last three years, since the eighth IVF cycle for this patient, I have had the occasion to evaluate several patients who have been to the IVF center that performed the eight IVF cycles on this patient, and to this date, the semen analysis that they perform does not include this simple inexpensive HOS test. In fact most IVF centers, for reasons not clear to me, do not perform this test.

Case 3

A 35-year-old woman with four years of primary infertility presented for IVF and ICSI. The reason for the desire for IVF with ICSI was because of a male factor problem related to antisperm antibodies (82% IgG and 77% IgA) using the direct immunobead assay and a low HOS test (47%). Typically IVF with ICSI corrects both defects and allows normal pregnancy rates following embryo transfer [12-14]. However this woman kept making highly fragmented embryos and failed to conceive following 12 IVF-ET cycles at our institution and following four at two other IVF centers [15].

Antisperm antibodies typically impairs fertility by preventing the sperm from progressing in the cervical mucus and by inhibiting attachment of the sperm to the zona pellucida [16]. A subnormal HOS score leads to implantation defects [9, 10]. There are no data showing that these defects lead to embryo fragmentation.

Though highly fragmented embryos do not necessarily lead to implantation failure, we considered that this could be the cause of her refractory infertility despite IVF-ET [17, 18]. We tried various nuances to see if we could achieve a pregnancy in this couple using both their gametes, e.g., transferring frozen-thawed embryos in the absence of COH (as in case 1), low-dose gonadotropins and fresh embryo transfer, and lymphocyte immunotherapy [7, 19-21].

We advised the couple that in their case the most likely cause of the refractory infertility was related to the embryo fragmentation problem. Theoretically the problem could be related to an oocyte or sperm factor or both. At our institution we have for many years used oocytes from infertile donors as the source of oocytes from recipients [22]. In fact, we have demonstrated that these eggs are just as likely to form embryos that lead to successful pregnancies in recipients as eggs from paid donors [23].

To help determine if the problem was a sperm or oocyte issue we asked the woman if she would be willing to be a shared oocyte donor. Most of the time recipients will choose a donor who has a tubal factor or definite male factor but it was unlikely that anyone would select this woman because of so many failures to conceive despite the transfer of many embryos plus the fragmentation issue (all these details would be made available to the potential recipients). For research purposes we offered free IVF to any recipient who would select this patient's eggs.

This infertile donor who had failed to conceive despite 16 previous fresh embryo transfers and many frozen embryo transfers had 49 oocytes retrieved following COH [15]. The donor fertilized 17 of the 24 oocytes and all 17 were cryopreserved at the 2 pronuclear stage because of fear of developing ovarian hyperstimulation syndrome [24]. There were 13 of these 17 embryos transferred over three frozen ET cycles (4 were discarded for cleavage arrest). All 17 embryos had > 25% fragmentation and none of the transfers resulted in a pregnancy.

The recipient received 25 oocytes which were fertilized using conventional insemination and 13 fertilized. Three embryos were transferred on the donor retrieval cycle with ≤ 25% fragmentation but she did not conceive. Subsequently five frozen embryos were thawed and three were transferred and two discarded because of cleavage arrest. She conceived triplets and all three were successfully delivered at 35 weeks. Two of three embryos transferred had ≤ 25% fragmentation.

Because of having triplets, the couple decided when they were one year old to donate the remaining eight embryos to our donor embryo pool [25]. The new donor embryo recipient thawed all eight embryos and only one had > 25% fragmentation (but < 50%). Three embryos were transferred, two were discarded for failure to cleave, and three were refrozen. She failed to conceive on that

cycle but subsequently transferred the three remaining embryos and all three implanted. There was enlargement of the yolk sac on one of the three gestations which was suspicious for a chromosome abnormality. Chorionic villus sampling of the gestation was performed and chromosome analysis revealed trisomy 21. Multifetal selective reduction was subsequently performed and she delivered viable twins at 37 weeks.

These data have clearly shown that at least in this case the problem of embryo fragmentation was related to a male factor problem. Furthermore, at least in this case, the fragmentation was associated with implantation failure [15].

Though the option of changing gametes was presented to this couple many times after they had had several failures, the success of the recipients with different sperm convinced them to try donor sperm. They failed to conceive after two cycles of intrauterine insemination with donor sperm so they proceeded to IVF with donor sperm.

Though they proceeded with IVF with donor sperm they chose to freeze all embryos to allow them to try another retrieval IVF cycle with the husband's sperm. However the mature eggs failed to fertilize so they decided to thaw some of the embryos created by donor sperm which were frozen at the 2 pronuclear stage. They transferred four embryos – two 8-cell embryos with < 25% fragmentation, a 6-cell embryo with < 25% fragmentation, and a 7-cell with 25-50% fragmentation. The patient conceived and subsequently delivered a full-term healthy baby.

Discussion

A 45-year-old infertile woman with a high day 3 serum FSH level sought infertility help. She was told that her prognosis was extremely poor and that she should consider donor oocytes. However, donor gametes were not an option due to personal reasons. She and her husband were diagnosed with a luteal phase defect and mild male factor problem, and treated with intrauterine insemination and progesterone supplementation in the luteal phase. The patient conceived at age 46 on her 14th treatment cycle and had a successful delivery [26].

In the aforementioned patient her insurance covered all the IUI cycles and she did not have to undergo any risky, invasive or painful procedures. Thus she had nothing to lose by continuing treatment. However, IVF requires daily injections, risk of ovarian hyperstimulation, very frequent monitoring and great expense.

Nevertheless, with perseverance all the couples achieved successful pregnancies with IVF-ET. Lessons to be learned by couples from these anecdotes, are to be patient up to a certain number of cycles because "bad luck" can only explain a few failed cycles. If the treating physician has no new plan, the couple should challenge the treating physician to consider possible reasons for failure and treatment options. If patients covet their own gametes they should not allow the "quick fix" suggestion that maybe the eggs are not good and thus they should consider donor eggs or adoption. Indeed, in case 1, where the drugs used for COH caused the problem, the use of donor eggs would have worked because of the lack of use of COH drugs, but success could be achieved with the preferred "self" gamete by merely doing frozen embryo transfer. The patient's decision to try other IVF centers if a couple of cycles in a given center were not successful, hoping that the new center might approach the problems with new insight leading to success makes sense. However, she should have considered getting an opinion from another IVF center before going through so many failed cycles in the third IVF cycle with so many embryos transferred. Case 2 showed a loyalty to one given IVF center that defies logic.

From the physicians' standpoint, these anecdotal cases illustrate the importance of avoiding complacency. With the risk and great expense of the procedure, it behooves the treating physician to spend some time in considering reasons for the failures and not merely try the same thing that failed over and over. For case 1, one cannot fault the first two IVF centers since chance alone could explain even three failed embryo transfers. Though I still think that the second IVF center should have considered trying something different before proceeding with cycle 4, e.g., frozen embryo transfer. Nevertheless, why they never tried the less invasive and far less expensive frozen embryo transfer defies logic. However one must seriously question why the third IVF center did not do anything differently not only for cycle 5, but was willing to proceed with no logical change in the procedure for five additional IVF cycles. Not only did she fail cycle number 5 but she failed with the transfer of 12 embryos. Yet they continued to transfer 12 embryos for five additional IVF cycles without making any changes!

In my opinion in one circumstance, e.g., case 1, the third treating physician should have insisted that the couple get another opinion from another IVF center to get a fresh view and he should have guided them to a facility that specialized in finding and correcting reasons for repeated failures. The referring center could offer their help in considering the proposed new solution to advise the couple as to whether it would seem reasonable and whether the referring IVF center could carry out the suggested change or would the couple be more advised to continue with the new center. The reluctance of the physician in case 2 to proceed with ICSI with the low HOS test is an example of the arrogance of some physicians and the need for patients to get second opinions earlier.

The couple in case 3 was very happy that they had a baby with donor sperm. However they were not ready psychologically to use other gametes until they were completely convinced that this was the only way. Nonetheless case 3 illustrates that it "takes two to tango" and one cannot always assume that if embryos do not implant the problem must reside with the woman's ovaries or uterus. The couple was constantly advised of the low likelihood of success with their own gametes and/or uterus after many failures and the gametes were more suspect because of fragmented embryos. Nevertheless, I tried various new approaches, and when the couple tried another IVF center, it was following my suggestion. Nevertheless, when they failed, I was very willing to take them back.

I believe that the chance to help a given couple with their dream supersedes the business objectives of some IVF centers. With published statistics on pregnancy rates by the Center for Disease Control, some IVF centers would

stop offering more IVF attempts not necessarily for the benefit of the couple, but rather not to sacrifice their published pregnancy rates which could detract from future business from other couples who may seek an IVF center with a high success rate.

Case 3 also illustrates the importance of the treating physician to do due diligence and not guess at whether to use donor eggs or a gestation carrier for repeated failures but to consider some method to determine the real source of the problem. The expense this couple had trying with their own gametes was considerable but it would have been "adding insult to injury" if they wasted even more money on very expensive donor oocyte cycles before finally proceeding to donor sperm.

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