Editorial Article

A 59-year-old woman gives birth to twins - when should a fertility specialist refuse treatment?

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Summary

Objective: To review cases of infertility where despite extremely low odds of success and potential risks to the woman if she became pregnant or to the fetus, the couples elected to take a chance to fulfill their dreams of having a baby. *Materials and Methods:* Six cases are described: case 1, a 59-year-old woman with hyperstimulation and intramuscular fibroids compressing the uterine cavity who wanted to be a donor egg recipient; case 2, a 59-year-old woman desiring a second transfer of sibling frozen embryos who had previously conceived with donor eggs at age 57; case 3, a 33-year-old woman with a subseptated uterus and cervical abnormality from intrauterine diethilstibesterol exposure plus hemoaphilia trait, and only 25% of her liver remaining from a previous partial liver resection; case 4, a woman with an unicornuate uterus refusing reduction of her twins to a singleton; case 5, a 39-year-old woman willing to try again to have her first live born child with a history of a large macroprolactinoma that was resected but markedly enlarged in her previous pregnancy despite bromocryptine therapy; and, case 6, a woman willing to try a unique experimental therapy with extremely high thyroid stimulating immunoglobulins to inhibit severe intrauterine growth retardation and potential premature synostosis for her condition of Hashimoto's disease. *Results:* Cases 2-5 all had successful outcomes. Case 1 was never given the chance for donor oocytes since she was rejected by a majority vote of our physicians because of the fear of a malpractice suit. *Discussion:* If a couple understands the potential risks and the low odds of success, they should be given the opportunity to fulfill their dreams of having a baby. However, treating physicians are under no obligation to take malpractice risks.

Key words: Advanced maternal age; Premature ovarian failure; Uterine anomalies; Intrauterine growth retardation.

Introduction

Patients have certain health issues that may make them seek help from physicians. The role of a physician is to make an assessment of the condition and offer advice on treatment options; the chance of successfully fulfilling the patient's goal, what the risks and costs would be for various therapies and their likelihood of success. Then given these options and after the physician ascertains that the patient truly understands the risks and benefits of these treatment options the right thing to do in my opinion is to allow the patients to make the choice that suits them the most, even if that choice would not be the one that the given physician would make for him/herself or his or her own family.

Unfortunately in our litigious society, sometimes the patient's choice may make the physician quiver for fear of a lawsuit but if the decision made by the patients is best suited for them and is a legitimate option, the proper physician should not dissuade any patient from making that choice.

When it comes to achieving pregnancy in an infertile woman some physicians may consider that the need for a baby is not a true "medical reason" and thus should not be deemed an entity worthy of therapy that could put the patient at risk for harm or the physician at risk for a malpractice suit. However, there are many women who suffer so much from their infertility problems that given a choice would gladly give up their right arm to accomplish that goal.

A lot of time and money is invested in becoming a physician and one large law suit can end that physician's career. Thus a physician should not be censured if he/she chooses not to render a particular therapy that could work but could also lead to complications to the patient which the patient is willing to risk – but the physician is still not willing to risk – the patient may still turn around and sue the physician. However, we should not censure any physician willing to take the risk of a malpractice suit if the treatment could work but has risks – if the pros and cons of therapy have been properly explained to the patient.

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Case Reviews

Case 1

A 59-year-old woman with a history of hypertension and intramuscular fibroids partially compressing the uterine cavity requested to be an egg recipient. She was advised of both general risks for her age and specific risks that she had based on her medical history.

She was advised that 1) because of her chronic essential hypertension she had at least a 20% risk of superimposed preeclampsia with no current strategy to reduce this risk. In addition, she was at risk for placental insufficiency, fetal growth restriction, stillbirth and placental abruption that could result in a state of disseminated intravascular coagulation, heart failure, stroke, seizures, or possibly death. Furthermore, there may have been a need for iatrogenic prematurity that could have led to permanent neurologic disability in the child. 2) Because of her prior myomectomy she had an increased risk of a potential rupture of the uterus. These fibroids could also cause intense pain from degeneration, fetal growth delay with oligohydramnios, stillbirth, and the fibroids could also obstruct the birth canal or cause a deformation in the baby. 3) Her advanced maternal age, although she would obtain a donor egg and have in vitro fertilization with her husband's sperm, would still increase her risk of miscarriage, growth restriction from placental insufficiency, oligohydramnios, stillbirth, cesarean section, wound infection, postpartum endometritis, gestational diabetes and potentially maternal death.

Despite hearing all the risks the woman still wanted to proceed with the transfer of embryos derived from donor eggs and her husband's sperm. She stated that as a nurse in South Africa she had taken many chances with her life by treating victims during South African riots. She had been a midwife in South Africa and she stated that young women there have a greater risk of complications than she had at age 59 when she would deliver. She took chances of possibly dying from infectious diseases by treating patients with highly deadly diseases. Her question was why it is considered appropriate for a nurse to take chances with her life when it comes to helping other people but that when it comes to taking a risk to her own life to bring a child into this world that would fulfill her needs, it is frowned upon? She had no living children but had delivered one child who died at birth.

I decided to treat her and it made me reminisce about other infertility cases that presented with significant risks but the women were steadfast in being willing to take a risk to fulfill their dream. Unfortunately, I could not convince my other three associates that she had the right to take a risk as long as she was fully aware. Nonetheless, they were concerned about malpractice risks and since our practice works on a democratic basis I regretfully had to inform the woman that we could not include her in the recipient program.

Case 2

A 57-year-old woman who had had a baby with her former husband at age 33 was interested in having another child with her new husband who was 20 years younger. She was advised of the risks which were similar to the 59-year-old nurse/mid-wife from South Africa (case 1) except she did not have fibroids or hypertension. She did, however, have Graves' disease and was being treated with propylthiouracil. She came to our practice from another state because she had seen our case report in the literature of the first woman to conceive in the United States over the age of 50 with donor eggs [1]. In that instance the woman also had a much younger husband.

There was an opportunity to fertilize donor eggs that were appropriate for the couple but they had to be frozen because the woman had not as yet completed all the testing and consults required. These were all necessary to have obtained before a vote from the ethics committee.

Probably the most swaying argument that convinced the ethics committee for the Cooper Center for Reproductive Hormonal Disorders, was the fact that her husband was only 37, had no children from any other relationships, and no one would have had a problem with the reverse situation, i.e., a 57-year-old male trying to achieve a pregnancy with a 37-year-old female. Though one thought was to suggest a gestational carrier (and we did) we could not insist on it when the woman stated she did not have an extra 50-70 thousand dollars (she had checked into this option and this was her conclusion).

She conceived on her first frozen embryo transfer cycle (3 embryos) at 57.6 years of age. She delivered at 36.3 weeks a healthy baby girl weighing 5 pounds, 2 ounces.

We had advised her that the embryo transfer leading to her delivery would be the last time that we would do a frozen ET. However, she still had three left and she pleaded to have them transferred to give her child the chance of a sibling. Half of our doctors refused to do the transfer, but two agreed, and the remaining three embryos were transferred (a 9 cell, 6 cell, and an 8 cell embryo with ≤ 25% fragmentation). Another pregnancy was achieved though this time a dichorionic diamniotic pregnancy was obtained. We strongly recommended reducing it to a singleton. We explained that she would be just one month shy of age 60 and her chances of a successful outcome would be improved if she only had one child to carry.

She was advised that we had had a woman aged 54 who had conceived twins but terminated the pregnancy at the end of the first trimester because she was exhausted. However, without any religious or ethical concerns she decided to carry the twins.

Her pregnancy was complicated by placenta previa and placenta percreta. She delivered at 30.5 weeks a male weighing three pounds, six ounces and a female weighing three pounds, six ounces. Both children were doing well seven months after delivery.

The rest of this editorial will consist of cases where despite what seemed to be either impossible odds of either achieving a pregnancy or carrying one full-term, couples persisted in their dreams.

Case 3

A 33-year-old female lawyer who was married to a 38-year-old lawyer was advised from a major university infertility center that due to of her intrauterine exposure to diethylstilbestrol she would never conceive because of hostile cervical mucus of very poor quality. This was before the days of intrauterine insemination. Moreover her uterus had complex septae so that it seemed to be in five compartments. The case presented before the days of hysteroscopic surgery. She was told that even if she did conceive she could never successfully progress to term.

Furthermore she was advised that because she had only 25% of her liver due to a previous partial resection for a benign hepatoma that she did not have enough liver to sustain a pregnancy.

I advised her that I disagreed that 25% of a liver was insufficient and that it was possible to correct the cervical factor. However, I did agree that because of the septae there was a great likelihood of marked prematurity with adverse health consequences for the fetus.

The couple wanted to proceed despite the precautions. In fact the female partner advised me that she had a hemophilia trait and that her hematologist had told her that she could bleed excessively with delivery or cesarean section and advised her not to become pregnant. She still wanted to take her chances. The couple decided that they wanted to end the genetic passage of hemophilia. Thus they planned to do chorionic villus sampling and genetic testing for hemophilia. Since a heterozygote could not be detected, their plan was to terminate the pregnancy if she was having a female baby or if she was having a male with hemophilia.

She was treated with guaifenesin and ethinyl estradiol and human menopausal gonadotropins to treat the cervical factor and she used progesterone vaginal suppositories in the luteal phase [2, 3]. This therapy enabled the woman to attain an adequate postcoital test. She conceived on her second treatment cycle. The results of chorionic villus sampling showed a male without hemophilia. She delivered a healthy baby at 34 weeks.

Case 4

A 34-year-old woman presented with infertility related to having a unicornuate uterus. She had only one fallopian tube and it was congenitally obstructed. She had presented in the early days of in vitro fertilization and we had just developed a technique for embryo freezing [4, 5].

We only transferred two fresh embryos which failed to result in a pregnancy. Though we cautioned her that multiple births would not be a good idea based on her small uterine cavity, she elected to have three frozen embryos transferred because of the uncertainty that they would result in a pregnancy. We did not know if embryos could be successfully refrozen at that time [6].

The day after her frozen embryo transfer her godson, who was dying from hypernephroma stuffed a pillow under his shirt and predicted that she was going to become pregnant that cycle. He then stuffed a second pillow under his shirt and predicted twin boys.

She had a positive pregnancy test. Shortly after she had received the good news her godson died. Previous to the embryo transfer we had discussed multifetal reduction if there was more than one fetus and the couple agreed to have this procedure performed in the event of twins or triplets. However, they decided not to perform the reduction procedure in honor of their godson's prediction. She delivered healthy twin boys at 35 weeks.

Case 5

A 35-year-old woman with amenorrhea since age 18 and primary infertility sought help to become pregnant [7]. She was told that based on elevated gonadotropins at age 18 and 27 with estrogen deficiency that she had premature menopause. However, she had heard we had some success in inducing ovulation with normal pregnancy in some cases of hypergonadotropic amenorrhea, so she sought help in trying to conceive with her own eggs [7]. At this time donor oocyte programs did not exist.

Her follicle stimulating hormone (FSH) at age 27 was 78 mIU/ml. She was advised that because of the number of years that she had been in ovarian failure that it would not be likely to reverse the ovarian failure since the principle in inducing ovulation in these cases is based on the fact that in the early stages of apparent menopause there are some preantral or antral follicles still present. However, they are resistant to gonadotropins unless the elevated serum FSH is lowered and the down-regulated receptors are restored [8-10].

Just to confirm the diagnosis sera LH, FSH and estradiol levels were obtained. Very surprisingly the sera LH and FSH were < 1.0 mIU/ml and the serum estradiol was < 5 pg/ml. This prompted a measurement of prolactin which was very elevated at 975 ng/ml. Serum thyroid and cortisol levels were normal.

Computerized axial tomography revealed a large pituitary mass with suprasellar extension into both the sphenoid sinus and left middle fossa. Surgical and radiation therapy consults concluded that the tumor had grown too large for either treatment. She lost her vision in the meantime. There had been some early reports that bromocriptine (at that time known as CB154) might shrink macroprolactinomas. Indeed, 5 mg of bromocriptine per day did shrink the tumor by 50% allowing a transphenoidal hypophysectomy to be performed. Her vision returned.

Following surgery she remained on 5 mg bromocriptine per day. Though her serum prolactin levels were still elevated (ranging between 400-600 ng/ml) no growth of the macroprolactinoma was noted two years following surgery.

The woman returned at age 37 stating that she was now ready to try to conceive. She was advised that with the persistence of high serum prolactin that there was a good chance that the tumor could grow and that at that time the safety of taking bromocriptine during pregnancy was not known. Furthermore, she would require expensive gonadotropin injections (her insurance did not pay for them) and the likelihood of these drugs stimulating ovulation after 20 years of menopause was quite small since she probably had no more follicles left. Nevertheless, she wanted to give treatment a try. She stated that she had been told by the neurosurgeon and the radiation therapist that she was going to die. Though she was hoping that a pregnancy would not kill her she was willing to risk death again to have a baby.

She failed to ovulate or even respond to the first two treatment cycles. She still wanted to try a third cycle and surprisingly she did ovulate. Finally it took 4350 IU of human menopausal gonadotropins (hMG) to achieve ovulation. With high-dose hMG therapy she ovulated in five of her next six stimulation cycles. She conceived on her ninth treatment cycle but had a first trimester miscarriage after showing fetal viability on ultrasound at seven weeks. She conceived again her next cycle and successfully delivered a baby boy at 31 weeks. The boy was deemed healthy and was discharged from the hospital. Unfortunately, however, at four months of age while strapped in a car seat, the baby died from sudden infant death syndrome.

The woman had averaged 3950 IU of hMG per treatment cycle in her ten cycles of gonadotropin stimulation. Despite the continuation of bromocriptine during the pregnancy the pituitary tumor grew to cause a bitemporal hemianopsia (but it regressed again after delivery). Nevertheless despite the risk and the expense she elected to try again.

She conceived again on cycle 11 but had another miscarriage. She conceived in her next attempt, had a live fetus through the first trimester, but unfortunately had fetal demise in the second trimester.

In the next cycle she again conceived and delivered a full-term baby girl. The girl is now a very healthy teenager who is an Olympic quality ice skater.

This case was allegedly a woman in ovarian failure who 20 years later developed a macroprolactinoma that suppressed her elevated serum gonadotropins either by a direct effect of the markedly elevated prolactin levels and/or damage to the sensitive gonadotropin producing cells. However, with her response to gonadotropins so many years after apparent menopause, I favor that she originally had a gonadotropin and prolactin secreting tumor which eventually secreted prolactin exclusively. I do not believe that such a case has ever been previously reported.

Case 6

A 33-year-old woman presented with a history of primary infertility with oligomenorrhea. Her medical history was significant in that she had hypothyroidism treated with L-thyroxin replacement but she also had Graves' opthalmopathy [8].

She was treated with clomiphene citrate and progesterone vaginal suppositories in the luteal phase and became pregnant. She was discharged from our practice after successfully completing the first trimester.

She called the office when she was six months pregnant stating that her obstetrician disagreed with our estimated date of confinement. She stated that ultrasound showed she was only five months along. I informed her that I knew the precise date of conception and that she was showing signs of intrauterine growth restriction (IUGR). She was advised to inform her obstetrician and to come into the office to have plasma long-acting thyroid stimulator (LATS) tested. My assumption was that she had thyroid stimulating immunoglobulins which were unable to stimulate her own thyroid gland because of damage from Hashimoto's disease. However, the antibodies would still be able to cross the placenta and stimulate the fetal thyroid causing fetal thyrotoxicosis and IUGR.

Unfortunately the LATS test, which uses mouse thyroid membranes in the assay, came back negative. I was still convinced that she had human thyroid stimulating immunoglobulins but at that time the assay was still experimental. Serum was sent to Dr. D. J. MacKenzie's laboratory in Canada. Unfortunately I was advised that the lab was having some technical problems with the assay and results would not be available for months.

At 32 weeks the patient went into labor. However, the obstetrician insisted that she was only 28 weeks by fetal biparietal diameter and tried to stop labor. At 33 weeks she had a cesarean section for fetal distress, amnionitis and prolonged spontaneous premature rupture of the membranes. A female infant weighing 1,446 g with a developmental age of 33 weeks died at 30 hours of life of group B streptococcal septicemia. A serum thyroxin of the baby obtained four hours after birth was markedly elevated at 24.5 μg/dl (normal cord serum 10.9 μg/dl + 1.6) and the T3 serum triodothyronine level by radioimmunoassay was 230 ng/dl (normal 48 ± 1.6 ng/dl) [8].

The maternal levels of thyroid stimulating immunoglobulins came back extremely high from the MacKenzie laboratory. Dr. MacKenzie actually advised sterilization of the woman because of the risk of severe IUGR and premature synostosis.

The patient was advised of the recommendation. However, I told her that I had an idea, that to my knowledge had never been tried before, and that was to give her an anti-thyroid drug despite the presence of hypothyroidism to cross the placenta and thus treat the fetus. Otherwise her options were to adopt or true surrogacy.

The couple chose to try again with clomiphene citrate and progesterone in the luteal phase. She conceived and was started empirically on 150 mg propylthiouracil per day. At 36 weeks gestation amniocentesis revealed a lecithin:sphingomyelin ratio greater than 2:1. An elective repeat cesarean section was performed with a delivery of a live-born male with an apgar score of 8 and 8 at 1 and 5 min. The infant's weight was 2,530 g, head circumference was 33.5 cm and had a total length of 45 cm. There was no evidence of a thyroid goiter.

At four days of life the infant developed tachycardia and elevated serum T4 and T3 (> 32 μg/dl and 630 μg/dl, respectively). The infant responded within three days to treatment with methimazole and lugoliodine solution as evidenced by shrinkage to normal size of the goiter, and the tachycardia ceased. All medications were discontinued at four months.

This case illustrates that this woman, though advised that her next child could have serious complications, was willing to take a chance on a treatment that had theoretical merit but had never been tried before. We could say she was rewarded for her bravery.

Discussion

These cases illustrate successful pregnancies despite low odds of success. They also show that couples are willing to take some chances on their health or the baby's for the chance of the gift of life.

Obviously, since we attempted to help these cases, my own view is that if the risks and odds are meticulously explained to a couple, but they want to proceed with infertility therapy, they should be given the opportunity. Of course this should be done only if the couple seems to have a clear understanding of the risks and there is at least some chance for success even if the odds are very low. A physician has the right to deny a patient therapy if that physician is concerned about future lawsuits. However that physician should at least be honest and explain the reason for refusal to treat, and encourage the couple to seek another opinion.

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