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IVF's Role in Growing the Next Generation

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June 8th, 2018

In vitro fertilization (IVF) is an assisted reproductive technique (ART) that helps couples who struggle to become pregnant and have been used by doctors in millions of patients for over 40 years. However, there are many occasions where IVF does not end in pregnancy or live birth after the first cycle and many patients end up using multiple cycles of IVF. The collection of IVF cycles can have negative emotional and physical effects along with financial devastation on the patient. The negative consequences can be avoided if IVF is made more successful with newly implemented treatment methods. Through meta-analysis, some viable treatment options that are not already implemented include: monitoring and controlling the patient's body mass index (BMI), increasing the number of retrieved oocytes, and the use of frozen embryos and eggs. The research is presented in a paper published on the Reproductive Associates of Delaware website for the public, including doctors and patients, to view. With the research general to IVF patients, new treatment methods can be used in fertility clinics to improve the success rates of in vitro fertilization, therefore lowering the number of IVF cycles needed in a patient which thus can lessen physical, mental, and financial devastation.

Millions of women around the world are unable to become pregnant on their own every year. Many of these women look towards in vitro fertilization, or IVF, to build their family but only some succeed. To benefit those who do not succeed in becoming pregnant or having a live birth after IVF, there is room for growth to improve healthy single embryo production, or healthy singleton production, and eventually pregnancy rates. The patients with an unsuccessful first cycle depend on future cycles to bring them a child, but many cycles of IVF can have financial, emotional, and physical devastation to both the patient and their support system, such as a partner, family, or friends. More successes can take place if the body mass index, or BMI, is controlled and kept within healthy and optimal levels for IVF. Along with BMI, if more oocytes can be retrieved and frozen, there will be a greater number of healthy singletons and pregnancies. Implementing body mass index alterations and monitoring, increased number of retrieved oocytes per cycle, and the use of frozen embryo transfer can help create greater amounts of healthy singletons, pregnancy rates, and live birth rates, lessening financial, emotional, and physical devastation.

The current in vitro fertilization process that is used in fertility clinics consists of eight steps. The first step in an IVF cycle, the doctor must evaluate the patient through a series of blood tests and exams to see if and why the patient is infertile. The diagnosis leads to the second step where a treatment plan is developed based on the causes and severity of the infertility. Third, less invasive assisted reproductive technology is utilized, such as timed intercourse or intrauterine insemination, to attempt at pregnancy. If these cycles are unsuccessful, the next option, step four, is utilizing IVF and in this case, the doctor will prescribe a series of medications to begin ovarian stimulation. Medications include luteinizing hormone, follicle stimulating hormone (FSH), and human chorionic gonadotropin (HCG), the trigger shot given

within 36 hours before oocyte retrieval, paired with Lupron. Lupron is a drug that acts as an antigen to HCG and leads to a much less likely chance of developing ovarian hyperstimulation syndrome (OHSS) from a reaction to copious much HCG in the body. Fifth, medication is injected either in the abdominal muscles or in the gluteal muscles for 8-14 days at scheduled times daily or multiple times a day, depending on the patient's need for the hormone. Step six, after the allotted time medication period, the patient will return to a surgical center to have the matured eggs retrieved from the ovaries. In the seventh step, sperm is collected from the male and the eggs are fertilized in a laboratory. Lastly, after the fertilized eggs have matured to the blastocyst stage, the doctor implants the best developed and healthiest singleton into the uterus. Blood is drawn to perform a pregnancy test two weeks after the implantation to determine if the blastocyst has matured and began the fetal stage. Improvements can be made to the IVF process in order to increase healthy singleton production and eventually increase pregnancy rates.

For the data collection portion of the research, meta-analysis was utilized supplemented by interviews. Meta-analysis was the best option for the research because this allowed information to be gathered from multiple studies and established into one coherent piece that explains just how the IVF process can be improved. Additionally, access to human subjects and laboratories were not available for the testing. Studies were collected, analyzed, and data was taken and implemented into the research. Interviews were conducted with Dr. Joseph Osheroff from Shady Grove Fertility in Towson, Maryland, Dr. Kay Waud from Dominion Fertility in Arlington, Virginia (Appendix A), and Dr. Ronald Feinberg from Reproductive Associates of Delaware in Dover, Delaware (Appendix B). The interviews that supplement my findings were essential for narrowing the research and making it more precise. The information provided in the interviews helped to sculpt the thesis and provide details from clinics and experiences from

doctors practicing in the IVF field. The research greatly benefited from each of the studies that were included in the meta-analysis and the interviews collected from various professionals in the IVF field.

IVF has many different parts that can take a toll on the patient, especially financially. Just a single cycle of IVF can create financial devastation for the patient and their family. In vitro fertilization is a costly procedure that only a portion of eligible recipients can receive. IVF also does not always end with pregnancy after the first cycle which can lead many patients to need a second or more cycles. In 2015, medication and treatment costs for an IVF single embryo transfer and an IVF modified natural cycle reportedly cost between €4000 to €7000, equivalating to $4,924.52 to $8,617.91 (Tjon-Kon-Fat). According to a *CNN Money* article, the median middle-class annual income in 2016 was just above $59,000 (Luhby 1). A single cycle of IVF could cost between 8.34%-14.6% of the annual middle-class income, the same amount or more than that is spent on repaying loans, transportation, or savings ("Home Budget"). Considering these issues, it is difficult to consider how patients are expected to pay for multiple cycles of IVF when the first cycle is unsuccessful. Due to the extreme costs of in vitro fertilization, there are many couples who cannot pay for more than one cycle out of pocket, which, again, only a few patients can receive for IVF.

Not only do patients face financial devastation from IVF, but many of the patients can deal with emotional issues. The process of IVF can be stressful for many reasons including the idea of being infertile and needing medical intervention in order to become pregnant. The idea of losing a child can be one that many patients and couples have a very difficult time coping with since it is very similar to a miscarriage. Many women can feel like they are not "normal" when they need assisted reproductive technology to become pregnant, something that can also lead to

negative emotional reactions. In a 2010 study on the emotional health of couples undergoing IVF, 71.4% of patients reported symptoms of anxiety, 63.3% reported feeling depressed, and 61.4% stated that they felt helpless (Verhaak 1237). A different study found that those who did not receive gonadotropin-releasing hormone, or GnRH, also reported more unexpected crying, feeling more emotional, and felt more limited every day (Toftager 154). Additionally, quality and quantity of sleep were worse in patients who had been administered GnRH (Toftager 154). These studies along with numerous others prove that emotional troubles are created on both a small and large scale among IVF patients and their support systems and can be reduced if patients do not have to go through as many cycles of IVF and become pregnant in their first few cycles.

Many women who are undergoing undergo in vitro fertilization also have a high risk for physical discomforts due to medication injection and other complications during the cycle. For example, all women receiving ovarian hyperstimulation are at risk for OHSS. OHSS is a very painful syndrome that includes symptoms such as bloating and pain in the abdominal region, nausea, vomiting, diarrhea, hidden ectopic pregnancy, enlarged cystic ovaries, and ovarian cyst rupture or hemorrhage (Delvigne 77). Early OHSS peaks for women 3 days after the cancellation of the embryo transfer (Toftager 160). The reasoning for the cancellation is different for each patient. Late OHSS is found at peak 13-15 days after embryo transfer on the day of pregnancy testing for those patients who did follow through with embryo transfer (Toftager 160).

In order to limit these different physical, mental, and financial devastation, implantation, pregnancy, and live birth rates need to be increased. Women need to be able to have successful first, second, or third cycle of IVF in order to not need to endure and pay for additional cycles if those were not successful. The way to improve successful IVF rates lies in small changes to the

IVF process that will help in the long run of allowing more women to become pregnant fast. As stated before, these small changes including altering and montoring body mass index to reach a target range for the patient, retrieving a specific range of oocytes from the patient for fertilization, and finally implementing a freeze-all technique into clinics around the United States and around the world in order to enact frozen embryo transfers.

Body mass index, or BMI, is the calculation of weight (kilograms) divided by height (meters squared) that can help to categorize the state someone's body is in (ie. underweight or obese). A correlation has been found between increased body mass index and deleterious effect on estradiol level, follicle-stimulating hormone, quality of embryos, rates of clinical pregnancy, and live birth rates. Many risk factors during in vitro fertilization are also found from elevated BMI.

Body mass index can have a dangerous effect on estradiol levels when also administering human chorionic gonadotropin. Estradiol levels are a measure of hormones that quantify one's fertility, meaning that high estradiol levels result in higher fertility than those with low estradiol levels. A 2011 study stated that, "Compared with woman with low normal BMI, those with class I, II, and III obesity had significantly lower estradiol level on the day of human chorionic gonadotropin administration." (Shah 66). The study also concluded that low estradiol levels from high BMI can damage the ovaries, triggering poor oocyte quality which can lead to lesser embryo quality, lower implantation rate, and lower pregnancy rates (Shah 67). Peak estradiol levels were highest in women who had BMI of less than 20 kg/m^2 at 1424 and continued to decrease as BMI increased throughout the patients (Penzias 1034). The lowest peak estradiol levels were among the BMI 35 kg/m^2 or higher patient group at 1135. (Penzias 1034). With

increased body mass index, a patient's estradiol levels can decrease proving evidence that elevated body mass index can create fertility issues.

Follicle-stimulating hormone is also negatively affected by higher body mass index levels. Follicle-stimulating hormone, or FSH, is a hormone used to mature multiple eggs in the ovaries that are later retrieved, fertilized and implanted back into the patient and ideally, patients want high FSH. In the same 2011 study as before, FSH levels were highest in the BMI of 25-29.9 kg/m^2 group reaching 3,890+/-2,085 and FSH levels decreased as BMI increased, reaching as low as 3,884+/-1,820 (Shah 65). A different study has similar results and stated, "Day 3 FSH was also significantly different, with the BMI>25 group demonstrating significantly lower baseline FSH than did the BMI<25 group." (Loveland 383). In terms of highest FSH, doctors should urge patients to attain a BMI between 25-29.9 kg/m^2 through altering their weight.

A correlation has been found from the quality of embryos, rates of clinical pregnancy, and live birth rates to obesity and BMI. As BMI increases, the chance of pregnancy can decrease radically. Embryo quality (8-cell embryos, high symmetry, low fragmentation) was seen to be optimal for the normal weight group, decreasing as BMI increased (Shah 66). Additionally, as BMI increased past 25 kg/m^2, the live birth rates quickly diminished. The study was able to conclude that obesity has a negative effect on the outcomes of IVF and can create a problem regarding oocyte quality, the number of retrieved oocytes, live birth rate, clinical pregnancy rate, and spontaneous abortion rate. If BMI can be altered in order to be in a target range, then the women can have better embryo quality, increased rates of clinical pregnancy, and increased live birth rates and utilize fewer cycles of IVF.

Lastly, increased BMIs have a number of risk factors attached to them when using IVF. During an interview, Dr. Kay Waud from Dominion Fertility stated that many different risk

factors are present during an IVF cycle for women who have high BMI that are not present for those who have lower BMI. She said, "Number one is miscarriages, they miscarry more often. Number two, they are at higher risk for the crisis care agents. So they can get pregnant and then they miscarry. They're more infertile so they have a higher risk for not even getting pregnant, trying months and months and months in a row. This is something that I observe in my patients and we observe it internationally," (Waud). Many other studies, including those by Veleva, Wang, Matalliotakis, have corroborating data stating that miscarriages and spontaneous abortions occur in women with elevated body mass indexes and obesity than those who did not fit into those two categories (Veleva, Wang, Matalliotakis). It is evident that without alterations and monitoring, there is a likely chance that IVF will end in miscarriage for women who have high body mass index, causing them to use more cycles of IVF.

Along with BMI modifying and monitoring, the number of retrieved oocytes also influences the results of in vitro fertilization cycles in all women using IVF, regardless of BMI. Many studies and doctors have concluded that an optimal amount of oocytes retrieved for fertilization and then later for fertilization should be somewhere between 10–25 oocytes. A study from 2017 researching the ideal number of oocytes to be retrieved concluded that, "Among our cohort, we noted that more patients in group 5 [25 or more retrieved oocytes] achieved [greater than or equal to] 1 live births across all cycles (88 of 152 patients, 57.9%) and 2 live births across all cycles (23 of 152 patients, 15.1%) than in any other group."

(Vaughan 399). Later, the same study added, "We have demonstrated that a single, complete IVF cycle with high oocyte yield (>15 oocytes) can satisfy the average couple's overall reproductive goal of ≥2 live births, in 22.4% of cases. " (Vaughan 401). Clinical pregnancy and live birth rates were also found to peak in the group that had between 15 and 25 oocytes retrieved (Vaughan 402). The two rates also plateaued after the 25 oocytes retrieved group (Vaughan 402). A different study from 2014 found the same results, reporting, "They concluded that oocyte number is a strong correlate for LB [live birth] and that LB rate peaks at 15 … regardless of age," and also showed that there is a large difference in smaller numbers of oocytes retrieved than when larger numbers of oocytes are retrieved (Stewart 969, 970, 971). When 0–5 oocytes were retrieved, the live birth rate was 17% and when 11–15 oocytes were retrieved, live birth rates increased greatly to 39.3% (Vaughan 969). Lastly, a 2015 study also stated that "With one embryo transferred, the live birth rate paralleled the number of retrieved oocytes…," meaning that when there was an increased number of oocytes retrieved and one of those oocytes was fertilized and transferred, then there was an increase in live birth rates (Baker 932). These findings reflect the point that when more oocytes are retrieved for fertilization, pregnancy and live birth rates increase,

allowing for more women to become pregnant through IVF in fewer cycles, lessening the negative effects of IVF.

Aside from BMI and number of retrieved oocytes, pregnancy and singleton rates will be increased with the implementation of the "freeze-all" technique. The "freeze-all" technique is used when oocytes are retrieved after ovarian stimulation, fertilized, and then finally cryopreserved. After the retrieval, the patient waits through one menstrual cycle and returns to the surgery center where the frozen embryos have been thawed and are ready for transfer back into the patient to await implantation. This is different from a fresh embryo transfer, where the oocytes are retrieved, fertilized, and then administered back into the patient for implantation. Multiple studies and doctors have concluded that frozen embryo transfer, or FET, has better advantages and results when compared to fresh embryo transfer, emphasizing the need for implementation of the "freeze-all" technique into all fertility clinic in the United States and around the world.

Use of FET can increase pregnancy results by relieving the woman's body of FSH and other ovarian stimulation hormones. Due to the lessened amount of hormones being injected into the body, the uterus is better able to prepare for implantation and therefore creating a more likely chance that the singleton will implant (Waud). In an interview, Dr. Waud stated that she has witnessed in her patients, "the uterus is now not bombarded with 10,000 units of hormones for 10 days. So that's the difference between a frozen and a fresh transfer. It's not so much the quality of the embryo, the quality of the embryo is just the same. It's the fact that the uterus that you're transferring into is different." (Waud). The hormone alleviation also allows for a less likely chance of the patient developing ovarian hyperstimulation syndrome since the body is relieved of additional hormones (Feinberg). With the alleviation of the hormones, the

endometrium is able to develop more naturally in order to prepare for embryo implantation (Roque 160). In an observational experiment, fertilization rates were .02% greater for the frozen embryo transfer group than the fresh embryo transfer group (Aflatoonian 360). Later, it was found that the frozen embryo transfer group had a 7.3% higher implantation rate than the fresh embryo group (Aflatoonian 360). Lastly, the frozen embryo transfer group found to have 41.7% of patients with clinical pregnancy, 39% of patients with ongoing pregnancy, and 26% of patients with multiple pregnancy rates as opposed to the fresh embryo transfer group with 31% of patients with clinical pregnancy, 27.8% of patients with ongoing pregnancy, and 15.4% of patients with multiple pregnancy rates (Aflatoonian 360). These higher trends in the frozen embryo group show that fresh embryo transfer has more negative outcomes during IVF than the frozen embryo transfer group.

In addition to improved IVF results, frozen embryo transfer has many other benefits for both the patient and the embryo. In an interview, Dr. Feinberg from Reproductive Associates of Delaware discussed the many different advantages provided to patients and the embryos through FET that are more difficult or impossible to receive in fresh embryo transfers. First, the frozen embryos can be screened for chromosomal and/or genetic abnormalities (Feinberg). This allows for both the clinic and the patient to know about any chromosomal and/or genetic abnormalities in the embryo before implantation and pregnancy. If the embryo does have any abnormalities, the patient can decide whether or not they want to do with the embryo, whether they will transfer or not. Second, the patient can decide when to transfer the frozen embryo, controlling when the patient becomes pregnant (Feinberg). This also allows for the patient to, "preserve fertility for the future," and use the embryos later in life (Feinberg). Third, doctors are able to more easily, "treat underlying disease and gynecologic disorders [in the patient] before transferring an

embryo," (Feinberg). This can allow for better health in the present and future for the patient and the fetus during pregnancy. Lastly, The health of the mother and the fetus can be better monitored during the pregnancy (Feinberg). These advantages leave clear evidence that frozen embryo transfer, besides just improved pregnancy and live birth rates, is more beneficial to the patient and the eventual fetus.

With the implementation of these various options offered above, body mass index alterations and monitoring, increased number of retrieved oocytes per cycle, and the use of frozen embryo transfer into the in vitro fertilization process, greater amounts of healthy singletons, pregnancy rates, and live birth rates, are expected to occur. With the greater positive results of IVF, patients should not have to endure as much financial, emotional, and physical devastation. The three options have been proven by multiple studies and doctors to be beneficial to the IVF process. Possible errors in the data collection include quality of the studies used and the variety of studies used. The data was affected by the fact that not every study that has been published that fit the thesis of the research could be considered during the research process. If the research could be repeated, more focus would be put on narrowing down the research more quickly at the beginning of the research process and making sure that the sample sizes are viable for the final research. The research conducted here was just the intermediate steps to finding the perfect IVF process, therefore leaving room for more research to be done. The purpose of my research was to create the next stepping stone for more research to be conducted. In the future, scientists, doctors, and researchers alike must find new areas of the IVF process that can be improved upon. If these improvements can be made, women can become pregnant in the first cycle of IVF, therefore lessening financial, mental, and physical devastation created from further cycles of IVF.

In vitro fertilization is one of the most necessary and beneficial modern innovations in the medical field. The process has allowed for millions of women to become pregnant rather than resort to use of a surrogate or adoption. However, only a portion of the patients become pregnant, some in their first cycle of IVF, others in up to the sixth cycle. New implementations into the IVF process can allow for more women to have success when utilizing IVF in fewer cycles. When women are able to become pregnant through fewer cycles of IVF, then they do not have to suffer from greater degrees of financial, mental, and physical devastation. Body mass index altering and modification to achieve a target BMI, greater amounts of oocytes retrieved, and universal implementation of frozen embryo transfer in fertility clinics can help increase the chances of a woman becoming pregnant in one of her earlier cycles of IVF. Although more work needs to be done in the field, these improvements to the IVF process can help women achieve pregnancy quicker and keep their mental, physical, and financial health in better shape.

I would first like to thank Ms. Burns for her assistance in guiding my research and final product. I would also like to give my gratitude to Dr. Osheroff, Dr. Waud, and Dr. Feinberg who gave me their time and knowledge about my topic and their work.

Glossary:

Clinical pregnancy - pregnancy confirmed by evidence of pregnancy symptoms or at least one gestational sac (Zegers-Hochschild 2685)

Controlled ovarian stimulation - development of multiple follicles from the ovaries by use of stimulating hormones that will later by used to retrieve matured oocytes (Zegers-Hochschild 2685)

Cryopreservation - storage of matured gametes, zygotes, embryos, and gonadal tissue by means of freezing (Zegers-Hochschild 2685)

Embryo transfer - implantation of fertilized mature embryos into the uterus or fallopian tube

Fertilization - combination of an ovum and sperm to combine genetic data to form a zygote

Follicle stimulating hormone - a hormone used to mature multiple eggs in the ovaries that are later retrieved, fertilized and implanted back into the patient

Frozen embryo transfer - the use of a frozen embryo that was retrieved and fertilized in a previous cycle of in vitro fertilization for implantation (Zegers-Hochschild 2686)

Gonadotropin-releasing hormone - a hormone used to prevent ovulation for a short period of time

Human chorionic gonadotropin - hormone released by hypothalamus that helps produce luteinizing hormone and follicle stimulating hormone (Osheroff)

Implantation - attachment of a blastocyst usually to the endometrium five to seven days after fertilization (Zegers-Hochschild 2686)

In vitro fertilization - "an ART procedure that involves extracorporeal fertilization" (Zegers-Hochschild 2686)

Intrauterine insemination - the direct medical administration of semen into the uterus, typically a procedure done before resorting to in vitro fertilization

Luteinizing hormone - hormone released by pituitary gland that triggers ovulation (Osheroff)

Oocyte - matured egg/follicle

Ovarian hyperstimulation syndrome - bodily reactions occuring when the body becomes overwhelmed by the quantity of hormones that are being administered during in vitro fertilization; characterised in degrees of mild, moderate, and severe (Zegers-Hochschild 2686)

Singleton - one fertilized egg that is later used for implantation

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Appendix A: Dr. Kay Waud from Dominion Fertility in Arlington, Virginia

Waud: Hi, this is Dr Kay.

Erin: Hi, this is Erin Edwards.

Waud: Oh hi Erin. How are you doing? Thanks for calling me. Of course I completely forgot. I had a couple of surgeries this morning and I was working on something. Sorry. You did the right thing. So let me just pull up your questions. Let's see. How come you're interested in this like why did you focus your research on this?

Erin: So my stepmom and my father actually they did ivf about a year ago, no they started it about two years ago and they did five or six cycles and right now my step-mom's nine months pregnant from ivf.

Waud: There's always a reason. OK, let's see. Do you want me to read the questions and answer them for you or how do you want to do, do you have specific ones? How do you want to go about this?

Erin: Um, well those are just the questions that I had. You can just tell me your answers if you want. Is it OK if I do an audio recording?

Waud: Yeah sure, I don't mind.

Erin: OK. So you have the questions in front of you, right?

Waud: So, well, um, I was actually interested in woman's health and mostly endocrine, what you're interested is infertility, but that's only part of what we do. Um, our general title is actually reproductive endocrinology and infertility and what we would is mostly hormones and the study of hormones which is considered endocrine and that's what I was interested in and I was interested in women's health and then one thing led to another and then I became interested in women's reproductive endocrine, which goes hand in hand with infertility. That's how it happened. So my main passion was to start with was woman's health and endocrine, reproductive endocrine. And then that translated into ivf. That's how I got interested in this. This was way before medical school. I was doing a research and actually this was all in Southern California. Um, I was actually a physics professor at a university and then interested in biology and genetics and started volunteering at the genetics labs and um, that's worked with endocrine and um, there is formulas and stuff and that's how I got interested in Stella's like, I don't know, 15 years ago. So that's my story. And now I'm, I'm mostly do, um, IVF because infertility is mostly what we do for a woman. So what are some predictors, that is a good

question. Actually, I didn't know where you got this from, but that's really good. What are some predictors that we use when consulting with patient about their likelihood for success with ivf? Now, when it comes to ivf or any reproductive outcomes like, you know, for me to be able to close my eyes and tell if somebody is going to be pregnant or not pregnant, it's a woman's age.
Erin: OK.
Waud: Well, it's a little more complicated than that. For instance, I don't know what your stepmom's situation is, you could be 50 and you potentially get pregnant. You hear on the news like you know, 55 year old Janet Jackson gets pregnant. It's not with her own eggs though. So that's the thing. So it's age of the egg and in biology egg, the cell, we call it an oocyte. So that's what the term is used. So the age of the oocyte is the major predictor for who's going to get pregnant. So you can give me like, I don't know, hundreds of patients in front of me and doesn't matter what the difficulty of getting pregnant is, I know if I'm going to get somebody pregnant, that's the youngest patient.
Erin: Yeah.
Waud: OK. So that's, that's the number one predictor. Number two is the fact that if they had been pregnant before, let's say somebody was pregnant when they were 22 and then something has happened and now they're 40 years old and they're struggling to get pregnant. And I have another 40 year old who's never been pregnant before. Between the two, the one who's been pregnant before is more likely to get pregnant again.
Erin: OK.
Waud: OK?
Erin: Yeah.
Waud: But that's it. There's no other, you know, detects it. Maternal age is the number one predictor for who's going to get pregnant without treatments, with or without treatment.
Erin: Yeah.
Waud: That's the bottom line. That's always the right answer. The woman's age or the age of the egg. And yet if you comparing like, there's egg donation. I can get like potentially a 20 year old's eggs and fertilize it and put it in a 50 year old. Then it's the age of the egg. If I get it from a 20 year old, 50 year old woman was getting 20 year old's egg will get pregnant, it's more likely for her to get pregnant than a 40 year old woman getting pregnant with their own eggs.

Waud: OK. So let's see. Next question. Many studies suggest that a woman who have a higher BMI, have a greater chance of having clinical pregnancy- Absolutely true. Is it something you're observing? Yeah. Yeah. This is true. Period. I mean this is number one question. We asked two questions I ask my patients. Well, you know, even on the form like how old are you? Have you been pregnant before and what's your height and weight because their BMI, even overweight women that have difficulty getting pregnant and in OB school been open to, you know, the BMI of 30 plus definitely have. So there the whole list of things that are at risk for. OK, what number one is miscarriages, they miscarry more often. Number two, they are higher risk for the crisis care agents. So they can get pregnant and then they miscarry. They're more infertile so they have, they have higher risk for not even getting pregnant, trying months and months and months in a row. Um, so yes, this is something that I observe in my patients and we observe it internationally in a group. There are other studies such as one on European journal OB-GYN surgeon says no correlation, which may be mit chemical payments who ate. Um, I'm not, I'm not aware of this study, uh, but I can tell you most studies that are randomized, um, are they put a woman with a bmi of 30 and above, they still be someone at higher risk for, like I said, I'm in fertility miscarriages, um, recurrent pregnancy loss. And then once they do get pregnant, their children to fetuses are at higher risk for aneuploidy. I'm malformations, chromosomal abnormalities, um, what have you. So if you have, you know, specific if you want to have specific information more and that I'm happy to give you that. But, uh, that's the one in our guidelines. Happy to check, check into this specific article that you're referring to. Um, and also chemical pregnancy rate. I don't know what they mean by that. We usually are outcomes are live births or miscarriages. I don't know what they mean.

Erin: That study had a lot of things that were not great about it. And so I just tossed it to the side and it was like, you know what, I'm not going to use this one a because a lot of it didn't make sense.

Waud: I mean, there's not even a question that's a high BMI. Elise to um, intro to fertility and increases chance of miscarriage influences patients. Yeah. Before optimum amount of faith that we better optimize. There have been studies for this are really great randomized controlled trials out there. I spend maybe over 20 years that they've been out there. So it's, it's a confirmed over and over again. The optimum number, somewhere between 10 to 12. If you gets more than that, that's fine. But that does not increase the birth rate and if you get less than that, your live birth

rate will decrease. So it's like almost like a sweet spot and 10 to 12, or 10 to 14 is kind of the range we are looking for, that's the optimum amount of oocytes we get, we want to get.
Erin: OK.
Waud: If you get 25, it does not mean you're gonna get better live birth rate.
Erin: OK.
Waud: In my office, has there's been a correlation between the use of frozen eggs/embryos? So yeah. So now there's no difference. So that these are two different questions. I want you to understand the difference. So now there is no difference if they get the fresh eggs and then fertilize them, make the embryo, transfer versus I saw a frozen oocyte, fertilize it, and then transfer it. So there is no difference between frozen and fresh oocyte fertilization. OK. However, once you make the embryo there's a difference. If you make the embryo and transfer it in a fresh cycle versus if you make the embryo, freeze it, and then later on thaw it and transfer it in a frozen embryo cycle. Now the frozen embryo transfers are found to be more successful than a fresh embryo transfer.
Erin: Yeah.
Waud: OK. And the reason for that is, there are a lot of reasons, but one of them is during the stimulation, right? When let's say, you take a woman and you give them a lot of stimulation medication, their uterus, I mean you're trying to get all the eggs from the ovaries, but separate from the ovaries, all that estrogen and all the other hormones that effect the uterus as well. So it's not a natural environment for the uterus to be. If you take that freshly made embryo and put it in that uterus, we have found that the success rates were pregnancies, little less implantation rates are lower. So instead what we do is like we make the embryos and we freeze the embryos and then the woman comes back with a more normal or natural cycle than she would get pregnant, let's say naturally on her own. If you transferred those frozen embryos, froze them and transfered them, then she has higher chances of getting pregnant. Does that make sense?
Erin: Yeah, that makes sense.
Waud: OK, but there is no different between utilizing frozen eggs versus fresh eggs. Let's see. Other studies suggest that the overstimulation use an ivf followed by another and another cycle of overdoses paired with implementational stuff. I don't understand this. What's the question?
Erin: That's just what I found from the studies. Most of the studies that I've read is that it's pretty much just what you just said is that the AU center achieved and then fertilize once they're freeze

and then a woman does another cycle of hormones and then they implant the frozen embryo, the welding, the now thawed embryo, embryo that was frozen. Um, there's a higher implantation rate and then pregnancy rate.

Waud: Here's the thing that the embryos and just like the eggs, they’re the same, there’s no difference between fresh or frozen. The difference is the fact that the uterus is now not bumbarded with 10,000 units of hormones for 10 days. So that's the difference between a frozen and a fresh transfer. It’s not so much the quality of the embryo, the quality of the embryo is just the same, it’s the fact that the uterus that you're transferring into is different. So that's what makes the difference. And then do I have other suggestions for resources that I think I did, um, give you that. Um, that one I had about six friendships and stuff like that when we were freezing. I exciting. Um, I know there's so many resources. I'm happy to give you something, but I don't know what steps and what specifically you're looking for. I can definitely send you something about the Bmi because that's definitely interesting how, um, you know, how interested people. I was going to know, would you have any specific areas that you want resources on?

Erin: Um, well for my research I'm focusing on BMI, the might of the amount of retrieved and FET versus fresh.

Waud: See, I can find articles on those ones.

Erin: OK. Thank you so much.

Waud: Of course. Then let me know if you have any further questions.

Erin: OK, thank you.

Waud: My pleasure.

Appendix B: Dr. Ronald Feinberg From REproductive Associates of Delaware in Dover, Delaware

1. How did you first become interested in the IVF field?

I've never been asked that question! When I was a young medical student in 1978, big news came out about the birth of Louise Brown in England, the world's first IVF baby. This was a landmark medical achievement of the 20th Century, which happened after many attempts by Drs. Steptoe and Edwards to attain success with IVF. The birth of the first U.S. IVF baby Elizabeth Carr occurred a few years later, and as I was graduating from medical school at Penn, the first IVF births in Philadelphia were announced by Dr. Mastroianni, a future mentor to both Dr. McGuirk and me. So I would say those amazing events during my early medical education had a big impact on my future career goals!

As IVF gained traction around the world, one of the key questions that needed to be understood was how and why just a small percentage of embryos are able to implant in the mother's uterus. I became fascinated with that question while an ob/gyn resident, and ultimately devoted about 10 years of my career to being an embryo implantation researcher. One important theory proposed was that both the embryo and the uterine lining (the endometrium) needed to produce key molecules at the right time and place in order for successful embryo implantation to occur. In addition, we believe that embryos destined to successfully implant need to have the right genetic and metabolic machinery within their rapidly developing cells.

I've been a Reproductive Endocrinologist for about 25 years, and continue to be fascinated by all the laboratory and clinical factors that lead to IVF success. And I believe there is still much more to learn!

2. What are some predictors that you use when consulting with patients about their likelihood for success with IVF?

It is now well established that a woman's age is a very important predictor of the genetic and metabolic health of their eggs, and ultimately the embryo. (The maternal genes and mitochondria direct the earliest stages of egg and embryonic development). We do know that the chances of "taking home" a baby from IVF is about 8-10X higher for a 30 year old woman compared to a 42 year old woman, and that this is likely due to various age-related changes that occur in the ovaries. Many of our patients have a hard time understanding why this should be

the case, but multi-year statistics kept by the CDC and SART support the fact that age is critical to success.

Other clinical factors are less clearcut. A male partner with very poor sperm parameters often creates a negative prognosis. Other female clinical factors such as endometriosis, fibroids, 'swollen' fallopian tubes (called hydrosalpinges), extremes in weight (both over- and under-weight), and concomitant medical problems could all impact the chance of success. Our practice has taken great pride in trying to help women overcome these problems, whether via surgery and/or lifestyle change, to improve each patient's IVF prognosis.

Unfortunately, one factor that impacts our patients' ability to proceed with IVF relates to affordability. Even though it is almost 40 years since the birth of Louise Brown, IVF care still involves a large team of experts to individually help each patient — doctors, nurses, lab professionals, coordinators to name a few — and that makes care quite expensive. The medications required are also quite costly. IVF and fertility care have generally not been given the same important status in the healthcare industry as many other health problems, and so the majority of future parents needing care in the U.S. do not have the necessary insurance coverage to proceed.

3. Many studies suggest that women who have a higher BMI have a greatly decreased chance of having a clinical pregnancy. Is this something you observed in the patients that you have treated?

While it is generally accepted that a high BMI can negatively impact IVF success, we have not specifically evaluated that with our patients. It would require quite a lot of retrospective chart review in our practice to determine if BMI is a factor, plus a multivariate analysis would have to be carried out to correct for other potential factors (e.g. age and the other clinical factors noted above). Plus, even if we performed that research in our practice, I'm not sure we'd have enough data points to make statistically meaningful conclusions.

Having said that, extremes in BMI may also point to other underlying issues for women and men trying to conceive, i.e. nutritional status (quality and quantity of macronutrients), activity and exercise levels, stress, life happiness, relationship issues, genetic predisposition, insulin resistance and overproduction, and concomitant physical and psychological challenges. It's a rather complex set of factors and makes it difficult to "tease out" which factor is most significant.

Overall, we do counsel our patients about studies showing that high BMI is inversely proportional to success with IVF, and encourage them to make healthful decisions and changes whenever possible. We know that weight loss helps improve the ovulatory status for women with polycystic ovary syndrome (PCOS), so that suggests better ovarian health can occur when a woman's BMI is closer to a normal range.

a. There are other studies such as one in the European Journal of Obstetrics & Gynecology and Reproductive Biology that suggest that there is no correlation between BMI and chemical pregnancy rates.

I do not believe I know this article. If you send it to me I can take a look and possibly provide some comments.

4. Have you observed that the number of retrieved oocytes after ovary stimulation influences the patient's likelihood of becoming pregnant?

So again getting back to the Louise Brown story, she was conceived after Dr. Steptoe (the gynecologist) obtained just one egg from Mom Brown, and handed that one egg over to Dr. Edwards (the lab guy) for fertilization. For a couple of years that's how IVF was carried out — using the one egg most women prepare to ovulate each month. We also call that a "natural cycle", i.e. no stimulating hormones were given to drive the development of additional follicles and eggs.

Not too long after Louise Brown's success, IVF doctors considered the possibility that obtaining additional eggs from the same cycle might improve overall success rates. As such, IVF care entered an era where expensive drugs called gonadotropins (with the active hormone Follicle Stimulating Hormone — FSH) were used to achieve 'superovulation', i.e. the production of multiple follicles and eggs. That is still the approach most commonly used today, but IVF doctors have learned how to fine-tune the stimulation process. I believe most IVF doctors would agree that obtaining more than one egg can improve the chances of success, but no one really agrees on how many eggs are actually needed at the higher end, i.e. 5? 10? 20?

The reality is that quality of eggs is more important than quantity. So getting back to age, a 30 year old woman might only need 5 to 8 eggs to give her a great chance of having at least one baby, and maybe even a second or third child from frozen embryos. But a 40 year old who

generates 10 to 15 eggs (if that woman can produce that many) might have mostly abnormal eggs and/or embryos.

A woman's response to FSH stimulation of her ovaries is highly variable, but many IVF doctors are re-evaluating how many actual eggs are needed. Since the FSH medication is very expensive, this could sometimes affect whether a patient can even afford IVF. Our practice was selected for a presentation in 2016 at a national meeting where we showed data with 'mini-stimulation' IVF cycles (i.e. less FSH used), and demonstrated very good results in patients meeting certain clinical criteria.

As an interesting sidelight, the story of where FSH medication originally came from for IVF is a very fascinating tale, involving Italian nuns and large buckets of their urine!

5. In your office, has there been a correlation between the use of frozen eggs or embryos with the rates of pregnancy?

a. Many studies suggest that ovary stimulation used in IVF followed by FET (frozen embryo transfer) after the retrieval and another cycle of ovary stimulation paired with implantation of the now thawed embryo(s) increase odds of pregnancy.

Frozen eggs via vitrification are utilized more in the context of donor egg, and generally that approach works reasonably well. Many women are also choosing to freeze their eggs for future use, but there is not a lot of data yet on how well pregnancies will occur if/when those eggs are utilized for IVF. About 10 to 20% of women produce eggs that do not vitrify and/or warm successfully.

The technology for vitrifying and warming blastocyst embryos has become highly successful. Overall, 95 to 98% of blastocysts will survive those processes, and there are potentially more IVF pregnancies occurring from vitrified / warmed embryos than fresh embryos.

The use of vitrified / warmed embryos via FET has a number of distinct advantages over the use of fresh embryos: 1) opportunity to test embryos for their chromosomal and/or genetic status prior to transfer to the uterus (techniques called PGS and PGD); 2) ability to minimize or avoid a potentially-dangerous medical condition called Ovarian Hyperstimulation Syndrome (OHSS); 3) option to have control over when pregnancy will occur; 4) opportunity to preserve

fertility for the future; 5) stronger argument for sequential single embryo transfer; 6) ability to treat underlying disease and gynecologic disorders before transferring an embryo; and 7) maximize the health of the mother and fetus while pregnancy is underway.

Some IVF clinics are exclusively doing FETs and have eliminated so-called "fresh" transfers. We are keeping the option open for some of our IVF patients, particularly those who are younger and are going through mini-stimulation cycles. But we offer FETs and PGS to everyone. I'd estimate about 80% of our IVF patients are doing FET currently.

6. Do you have any other suggestions for resources that I should look into while I conduct my research?

RAD's communications and marketing team, led by our terrific Meghan Lynch, have compiled a number of very wonderful patient stories over the past few years, which provide a tremendous amount of information and education about the 'how and why' of decisions to utilize IVF for building families. For that resource, check out the archived stories at: https://ivf-de.org/seeds-of-success-stories/.