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Superior IVF Pregnancy Rates May be Achieved with a Disciplined Approach
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The mean United States IVF pregnancy rates reported to the CDC are approximately 25%. Few programs are reporting significantly higher pregnancy rates in excess of 60% for selected groups of patients. Superior IVF pregnancy rates result from improvements in multiple factors involving IVF including: more efficient patient selection; improvements in the IVF laboratory; improved media with blastocyst transfer; development of recombinant FSH; improved luteal phase protocols for uterine preparation; and improved embryo transfer technique. Clearly, the pursuit of enhanced ART pregnancy rates is multifaceted.

However, patient selection is the most important factor predicting success with ART. Female age is inversely proportional to IVF success rates due to increased ovarian gonadotropin resistance and deteriorating egg quality.1 Reduced egg quality presents at age 33 and accelerates after age 38. IVF pregnancy rates are 50% lower for women older than 39 compared to women younger than 35. Moreover, few women are successful with ART after 43. Fortunately, there are techniques to identify poor candidates for IVF prior to cycle initiation.

The most useful test to identify poor responders is a day 3 FSH and estradiol level.2, 3 If the FSH and the estradiol level are less than 10 mIU/ml and 70 pg/ml, respectively, then the patient generally has an excellent prognosis. If either level is elevated the prognosis is guarded, and for those with an FSH level greater than 20 mIU/ml, success rates are less than 1%. 4 For women with the intermediate test results, a more provocative test is appropriate, the clomiphene challenge test.5 This evaluation requires treatment during cycle days 5 through 9 with 100 mg of clomiphene followed by an FSH level on cycle day 10. If the FSH level is greater than 15 mIU/ml, the couple have a poor prognosis and egg donation is recommended.6

HRC performed a prospective randomized study evaluating the impact of ovarian response to gonadotropin stimulation on pregnancy rates.7 A pilot study of 61 women with fewer than 5 dominant follicles were determined to have a poor prognosis regardless of pre-cycle testing, 4/61. We subsequently randomized patients into two groups. In Group one, IVF cycles were cancelled using more selective criteria of at least 5 dominant follicles greater than 16mm on the day of hCG compared to the more commonly used criteria of less than 3 dominant follicles.

The results are posted in Table 1. Group 1 demonstrated higher pregnancy rates in all three age groups with the less than 35 years and the greater than age 40 years statistically significantly (submitted to ASRM October, 2001).
Therefore, using pre-cycle evaluations and ovarian response criteria, superior pregnancy rates may be achieved. However, patient selection alone will not suffice.
To enable ART programs to achieve ideal pregnancy rates it is important to have a state of the art IVF laboratory with an embryologist well trained in techniques of intracytoplasmic transfer, assisted hatching, preimplantation genetic diagnosis, and defragmentation of the embryo.

The laboratory requires state of the art incubators maintaining near physiologic conditions for the developing embryo as well as laminar flow with selective filters to remove organic solvents. In addition, specialized lighting protocols may improve clinical outcomes. More recently in selected patients, data has been presented suggesting delayed embryo transfer until day 5 following fertilization versus day 3 may improve implantation rates from 20% to 50%. With an average of 2.2 blastocysts transferred, pregnancy rates approach 70%. 8 This technique may provide superior pregnancy rates with fewer embryos transferred, minimizing multiple gestation rates.

This is especially important for women less than 35, the highest risk group for multiple gestations. Other factors contributing to higher pregnancy rates include improved medications for ovarian stimulation. The FDA has recently approved recombinant FSH for use in women undergoing superovulation, a product created by infecting hamster ovary cells with the human FSH gene. This provides a continuous source for highly purified FSH. Since these products were never in-vivo, there is no digestion of the glycoprotein. Recombinant FSH has minimal lot variation and contains 99.9% bioactive FSH. Studies treating women with recombinant FSH support improved pregnancy rates compared to urinary gonadotropins.9, 10

Recently, GnRH antagonists were approved to suppress ovulation during ovarian stimulation.11 Antagonists will likely replace GnRH agonists, a product requiring up to 10 days to suppress ovulation, improving ovarian stimulation efficiency. And finally, a vaginal progesterone gel (Crinone) has been developed for luteal phase support following IVF. The polycarbophil base maintains continuous absorption of progesterone, providing high progesterone concentrations within the uterine cavity. Crinone is undergoing investigation to determine the impact on IVF pregnancy rates.

HRC performed a prospective randomized study comparing two luteal phase protocols using Crinone for luteal phase support in frozen embryo transfers.12All patients received pre-cycle screening with sonohysterography and mock embryo transfers. Uterine cavity preparation was achieved with estradiol 2-4mg intramuscularly every 3 days starting cycle day 2 until the endometrium measured at least 8mm. In Group 1, women were randomized to receive 50mg of intramuscular progesterone in oil with Crinone 8% vaginally daily versus, Group 2, Crinone 8% vaginally twice daily. There were no significant differences in the mean ages of the women within the two groups.
Group1 had a higher success rate than Group 2, although not statistically significant. The combination provides a high local concentration of progesterone while maintaining physiologic concentrations of serum progesterone. This may provide more physiologic intrauterine and serum conditions resulting in higher implantation rates and pregnancy rates. Further investigation is required.

Finally, variations in embryo transfer technique among physicians has been demonstrated to have a profound impact on individual pregnancy rates in the same institution.13 For quality control, women should receive measurements of the length and the direction of the uterine cavity prior to initiation of an in-vitro cycle. HRC has been extremely successful performing cervical dilation prior to uterine preparation in patients with cervical stenosis, allowing atraumatic transfers. Pretreatment with vaginal cytotec 200ugm facilitates dilation in difficult cases. Aseptic technique during embryo transfer and prophylactic antibiotics with doxycycline may improve pregnancy rates.14 Uterine bleeding must be prevented during embryo transfer by avoiding contact with the uterine fundus, potentially increasing uterine contractility. In addition, ultrasound guidance during transfer may reduce transcervical embryo expulsion.15

In conclusion, maintaining superior pregnancy rates requires a multifaceted, disciplined approach. Previously mentioned factors may influence IVF pregnancy rates. Providing the highest possible pregnancy rates require continual evaluation of IVF laboratories, stimulation protocols, patient selection, luteal phase protocols and embryo transfer techniques. With multiple physicians, individual pregnancy rates must be determined since variations may occur with stimulation protocols and embryo transfer techniques.

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TABLE I

	< 35 years	**35-39 years**	**> 40 years**
Group 1	37/55 (67.3%)	24/49 (48.9%)	11/30 (36.7%)
Group 2	23/73 (31.5%)	36/112 (32.1%)	3/32 (9.3%)
p value	p < .01	p = .063	p = .024

	Pregnancy Rates (%)
Group 1	20/43 (46.5%)
Group 2	16/54 (29.6%)
p value	p = .13