



**CONCEPTIONS**  
REPRODUCTIVE ASSOCIATES  
OF COLORADO



# **Conceptions**

## **Reproductive Associates**

### **Testing and Treatment Information Guide**

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## **1. In choosing a center for IVF, is it appropriate to use success rates?**

SART (The Society for Assisted Reproductive Technology) has issued guidelines for advertising by ART (Assisted Reproductive Technology) programs (1). As a member of SART, Conceptions Reproductive Associates (CRA) adheres to these guidelines. These guidelines specifically state that comparison of success rates between practices is invalid. In fact, using SART Clinic Specific data for advertising/marketing that ranks or compares clinics or practices is unacceptable and is not permitted. The following statement must be included when quoting program statistics: “A comparison of clinic success rates may not be meaningful because patient medical characteristics and treatment approaches may vary from clinic to clinic.”

A clinic may exclude “poor prognosis” patients from attempting to use their own eggs with IVF, instead offering them only uterine insemination cycles or donor egg. If these women have a 20-30% pregnancy rate, then the programs that exclude them will have an overall higher pregnancy rate for that age category. At Conceptions, we treat women not statistics. We counsel patients regarding their prognosis at IVF with their own eggs based on age, diagnosis, endocrine and ultrasound testing. A lower pregnancy rate is acceptable to many couples who desire a chance to use their own eggs and sperm at IVF. At Conceptions, we give them that chance.

While keeping the above in mind, Conceptions pregnancy rates are outstanding and are available on our website. Google: [conceptionsrepro.com](http://conceptionsrepro.com)

If comparisons must be made, the most accurate way to do so may be to compare donor egg rates. Each clinic uses young donor eggs as a starting point, and high rates denote that the physicians are appropriately preparing the recipient surgically and medically; the physicians are stimulating egg production in the donor appropriately; they are retrieving the donor efficiently; and they are transferring the embryos with skill. Importantly, it also tests the embryology lab’s ability to efficiently culture embryos to the day 5 blastocyst stage. Conceptions donor egg pregnancy rates are consistently in the 65+% range.

## **2. Why doesn’t Conceptions Reproductive Associates offer Shared Risk Programs (“Money-Back Guarantees”) for Assisted Reproduction?**

After extensive review of the ASRM (American Society of Reproductive Medicine) Ethics Committee Report on Shared-Risk or Refund Programs in Assisted Reproduction (2), Conceptions elected not to participate with such programs.

The physicians at Conceptions view the treatment of infertility as a medical service and not an entrepreneurial business venture. As stipulated in the ASRM report, great care is needed in the implementation of shared risk programs. Patients should be aware that such programs only select otherwise good candidates for successful IVF. Patients are in fact paying a higher cost for IVF if they succeed on the first cycle.

Usually costs for pre-IVF screening and medications are not covered. In addition, a potential conflict of interest could develop in such programs with over-stimulation of patients to obtain a large number of eggs or transfer more embryos than is safe for the patient, fetus, and prospective offspring.

Shared risk programs are typically administered by a middleman who gets paid out of the profit margin of these programs. That profit is generated by those patients who participate. In addition, the patients who would most benefit from a money back guarantee are excluded at the outset, and the good prognosis patients that are offered enrollment would actually pay less if they pursue their cycles sequentially.

### **3. Is testing available for the woman that can help define prognosis for IVF?**

It is well recognized that age is an important factor influencing the ability of a woman to deliver a livebirth with her own eggs. In conjunction with age, we test for basal FSH and estradiol levels and often combine this with the clomiphene citrate challenge test which can further define decreased ovarian reserve. In addition, a resting follicle count (antral follicle count) can aid in predicting a woman's response to IVF medications and help in determining which IVF stimulation protocol may be appropriate for her. A slide discussion of these tests is available on our website ([www.conceptionsrepro.com](http://www.conceptionsrepro.com)).

Pre-IVF testing can add significantly to the overall cost of an IVF cycle. The goal of any medical test is to either make a diagnosis and/or have the ability to change the course of medical management. At Conceptions, we advocate testing that meets these criteria. Redundant, unproven or inefficient testing that will not change management adds to the overall cost of an IVF cycle without giving the couple any net benefit towards fostering a successful pregnancy.

### **4. Is there any value in screening with Antisperm Antibodies (ASA) before proceeding with IVF?**

Recently, Chiu published in a peer reviewed journal, Fertility and Sterility, a review and critique of the current English literature describing the effects of ASA on mammalian fertility (3). He concluded that current tests cannot differentiate the infertility-related ASA from those that do not interfere with infertility. The multiple reported effects that ASA may have on fertilization and implantation remains controversial. Because of the unknown actual role that anti-sperm antibodies have on in-vitro fertilization, advocating ICSI when they are present may actually result in an over-application of ICSI, which adds approximately \$2000 more to the cost of an IVF cycle. Furthermore, a patient's serum is not used as a protein source for the culture media, which avoids any potential ASA that could affect embryo development and implantation.

To the contrary, the Menkveld and Kruger system is one of the most important elements in determining if a couple would benefit from ICSI. Sperm morphology is

considered to be one of the most important parameters in evaluating the ability of sperm to fertilize an egg. Guidelines proposed by the World Health Organization (WHO) for normal morphology were published in WHO laboratory manuals of basic semen analysis in the 1980s and 1990s (4), and are still in use today in many fertility laboratories. However, with the advent of in-vitro fertilization technology, and especially the intracytoplasmic sperm injection (ICSI) technique for achieving egg fertilization with extremely compromised sperm samples, the values proposed by the WHO are now considered to be averages for the normal population and do not take into account specific minimum morphological parameters that still allow reasonable probability of conception (5).

In 1990, Menkveld and Kruger proposed a more strict system of evaluation of sperm morphology (6). Their method has since been shown to be not only a more reliable method of assessment of this aspect of the sperm analysis, but prognostic of the fertilizability of the sample in vivo (7) and in vitro (8). The Menkveld and Kruger system has been further refined over the years to include a more in-depth study of sperm head morphology, in particular the acrosomal component, which is especially important for the initial stage of fertilization of the egg. A relationship clearly exists between the integrity of this portion of the sperm head and sperm fertilizability (9).

Morphological evaluation of sperm by strict criteria has become the standard in clinics specializing in human assisted reproductive technologies. The Menkveld and Kruger system is practical, reliable and repeatable, and, most importantly, is predictive of sperm fertilizability. The data resulting from such an assessment are especially relevant to the clinician advising the infertile couple about the role of the male factor in their attempts to conceive.

##### **5. Is there any value in performing the post-coital test?**

A review (10) of the English language literature found the sensitivity (the ability to detect infertility) of the post-coital test to be 9-71% and the specificity (the ability to identify fertility) to be 62-100%. Wide ranges in the predictive value of normal and abnormal were also observed. The authors concluded that the post-coital test lacks validity as a test for infertility. Further, in a study (11) of 1135 total consecutive post-coital tests from a Duke University study population, 367 first cycles were analyzed. There was no difference in pregnancy rates regardless of whether there was no sperm in the mucus or an abundance of sperm in the mucus.

##### **6. What is the role of performing an ultrasound pulsatility index (PI) of the uterine arteries?**

There is compelling research (12) now available that acupuncture at the time of embryo transfer is a useful adjunct to a well performed IVF cycle. In a randomized controlled trial of 160 women, where age, diagnosis and embryo quality were equal in

both the treated and untreated groups, the group that had acupuncture performed had a 42.5% pregnancy rate and the group that did not had a 26.3% pregnancy rate.

For this reason, at Conceptions we offer in house acupuncture services to all of our IVF patients at the time of embryo transfer. Many women also use our consultants for a regimen of 8 weeks or more. Advocates of uterine artery pulsatile index sampling state that if the value is above a certain threshold, then they will advocate acupuncture. Because this costly test will not change our management recommendations, we do not routinely perform it on all couples. In addition, a well designed study (13) demonstrated that uterine blood flow does not reflect endometrial and sub-endometrial blood flow during the menstrual cycle and when using IVF drugs during a stimulation cycle, which is what the PI is purported to be measuring by those that advocate it. Finally, if uterine artery bloodflow is sampled in the morning four weeks prior to transfer, it remains a large vessel arterial system that may have different measurements that evening and/or four weeks later during the egg stimulation, endometrial maturation and/or at the time of embryo transfer. Because of these ambiguities and because it does not change our management recommendations, we believe that routine application of this test incurs an unnecessary cost and inconvenience for most of our patients.

#### **7. Is there an advantage to multiple hysteroscopies prior to an IVF cycle?**

At Conceptions, we evaluate the uterine cavity with saline ultrasound before the IVF cycle. If pathology such as a polyp or fibroid is found, we then proceed with operative laparoscopy to treat the pathology. Because only about 10-15% of women will have a previously unrecognized polyp, fibroid, or other uterine disorder prior to IVF, it allows 85% of couples to avoid the expense and inconvenience of what amounts to a normal diagnostic hysteroscopy.

Equally important, hysteroscopy as a screening tool cannot “see” the uterine wall like ultrasound can. For instance, it is important to know the size and location of all fibroids, and the relation that they have to the endometrial lining. Hysteroscopy cannot, but saline ultrasound can, identify and measure fibroids that are underneath the surface of the lining that may have an impact on implantation. At the same time, other entities such as adenomyosis (endometrium invading the uterine muscle) or fallopian tubes filled with fluid (hydrosalpinges) can be identified. If a septum or other irregularity is observed, 3D ultrasound can then be utilized to better define it.

Prior to the saline sonogram, we perform a trial embryo transfer with the same catheter we will be using during the actual embryo transfer. This allows us to measure and “map” the appropriate route to take through the cervix and into the upper uterine cavity. This helps ensure an atraumatic transfer when precious embryos are in the catheter during actual embryo transfer. By combining trial embryo transfer and saline sonography in a single office visit, we save the couple time and help conserve costs. Performing a diagnostic hysteroscopy, followed by an operative hysteroscopy, followed by a third hysteroscopy to ensure that the operative hysteroscopy was

successful is inefficient, more costly, and more time consuming for the patient. Likewise, combining saline ultrasound with screening hysteroscopy is also inefficient, redundant, and more costly to the couple. We believe that performing a screening saline sonography combined with trial embryo transfer, and then proceeding to operative hysteroscopy when abnormalities are found is the most efficient and accurate approach.

## **8. Should an endometrial biopsy for integrins be performed?**

Integrins are endometrial proteins that are involved in implantation. It is biologically naïve to think that one protein will make or break implantation. Indeed, many proteins in the endometrium have been identified as important to implantation (HOX-10 gene products, pinopods, TGF- $\alpha$ , HB-EGF, LIF, COX-2, IL-1 $\alpha$ /b, I-selectin). It is an evolutionary advantage that implantation be hearty and redundant, so that if the level of one protein is suboptimal, others may foster implantation. Further, if we biopsy for a given protein and it is absent or low, we cannot currently give a woman that protein back.

Integrins have been well studied. The amount of these proteins in the endometrium has been found to be diminished either when a woman has closed fallopian tubes that are filled with fluid (hydrosalpinges) or pelvic endometriosis. If a woman has hydrosalpinges, we remove them to increase her implantation rate and believe that the trapped inflammatory fluid retards implantation by several mechanisms, one of which may be integrin expression. If a woman has pelvic endometriosis, a long lupron protocol prior to IVF stimulation has been found to be advantageous. But the authors of this study state that it probably has to do with improved egg quality.

The advocates for integrin testing will perform the \$450+ test and if low, borrow the data from the endometriosis studies and treat with a long lupron IVF protocol. Not only do these women not have endometriosis or hydrosalpinges, but the long lupron protocol may not be appropriate for them with regard to egg production.

Perhaps a better empiric approach to a suspected implantation issue would be fostering increased perfusion at the time of embryo transfer with acupuncture. In the case of a thinner endometrium the use of adjunctive estrace (vaginal estrogen administration) and/or Viagra during the egg stimulation phase may be beneficial. A work-up for thrombophilia (subtle clotting defects in the woman that may disrupt implantation) and the administration of Lovenox (low-molecular weight heparin) or increasing folic acid as indicated may be appropriate. The empiric use of baby aspirin to favor vessel wall prostacyclin production (increased vessel wall relaxation) over platelet thromboxane production (decreased aggregation) is routinely employed. Increasing the dose of luteal phase progestin may also be considered.

Integrin biopsy may have applications in limited settings, but we believe that routine use is not warranted.

**9. Is it OK to proceed with IVF in the presence of pelvic endometriosis and or an ovarian endometrioma (cyst)?**

A recent study details the success of going to IVF even when endometriomas are present (14). If a woman has adequate antral (resting) follicles in the ovarian tissue around a pain-free endometrioma, a rational approach is to move forward with IVF stimulation. Surgical removal of the cyst prior to trying IVF may cause disruption in the function of the normal surrounding tissue even in the best surgical hands. Simply cutting a hole in an endometrioma and draining it has a high persistence/recurrence rate.

If a woman has a history of prior pelvic endometriosis or if a woman has an exam or history suggestive of endometriosis, she may still proceed to IVF without laparoscopy by taking advantage of a long lupron IVF protocol in selected cases.

If a woman has pain and a significant ovarian endometrioma, it is reasonable to take her to surgery and remove the cyst. Care should be taken to avoid damaging any of the surrounding normal ovarian tissue by utilizing a technique that limits the application of electrocautery to none or very minimal. Surrounding areas of the pelvis that are involved can also be treated.

**10. What is the role of the sperm DNA fragmentation assay?**

Sperm can be analyzed for fragmentation with the sperm chromatin structure assay (SCSA). A high fragmentation rate has been correlated with poor progression from day 3 (typically eight cell) of embryo development to day 5 (blastocyst) (15). The maternal and paternal genome (DNA) becomes fully active on day 3, so the contribution of the male DNA, and the deleterious effects of damage to this male DNA, can become relevant. But this is not the whole story. The maternal DNA and egg quality still play a profound role, and there is evidence to suggest that components within the egg can repair or overcome some of this subtle damage to the male DNA. This test may be relevant for couples that have otherwise unexplained poor progression from day 3 to day 5 for their embryos and would benefit from possible insight and/or would consider donor sperm if the sperm came back highly fragmented in the setting of healthy eggs, poor embryo progression and an unsuccessful cycle. Repeat sperm analysis after nutritional supplementation and elimination of any deleterious environmental effects, if present, can also be considered.

References:

1. Guidelines for advertising by ART programs, *Fertil Steril* 2004;82 No. 2:527-528.
2. Shared-Risk or Refund Programs in Assisted Reproduction, ASRM Ethics Committee Report.
3. Chiu et al., Clinical associations and mechanisms of action of antisperm antibodies. *Fertil Steril* 2004;83:529-535.
4. World Health Organization (1999) *WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction*. 4<sup>th</sup> edn. Cambridge University Press, Cambridge.
5. Menkveld, Wong, W.Y., et al. (2001). Semen parameters, including WHO and strict criteria morphology, in a fertile and subfertile population: an effort towards standardization of in-vivo thresholds. *Hum. Reprod.* **16**, 1165-1171.
6. Menkveld, R., Stander, F.S.H., Theunis, J.vW., Kruger, T.F., and van Zyl, J.A. (1990). The evaluation of morphological characteristics of human spermatozoa according to stricter criteria. *Hum. Reprod.* **5**, 586-592.
7. Ombelet, W., Menkveld, R., Kruger, T.F, et al. (1995) Sperm morphology assessment: historical review in relation to fertility. *Hum. Reprod. Update.* **1**, 543-557.
8. Donnelly, E.T., Sheena, E.M., et al. (1998). In vitro fertilization and pregnancy rates: the influence of sperm motility and morphology on IVF outcome. *Fertil. Steril.* **70**, 305-314.
9. Menkveld, R., Vermeiden, J.P.W., et al. (1996). Acrosomal morphology as a novel criterion for male fertility diagnosis: relation with acrosin activity, morphology (strict criteria), and fertilization in vitro. *Fertil. Steril.*, **65**, 637-644.
10. Griffith CS, Grimes DA. The validity of the postcoital test. *Am J Obstet Gynecol* 1990; 162: 615-20.
11. Bush MR, Walmer DK, Couchman GM, Haney AF. Evaluation of the postcoital test In cycles involving exogenous gonadotropins. *Obstet Gynecol* 1997; 89: 780-4.
12. Paulus WE, Zhang M, Strehler E, El-Danasouri I, Sterzik K. Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy. *Fertil Steril* 2002; 77 No. 4: 721-4.
13. Ng E and Ho PC. *Human Reprod* 2004; 19: 2385-90.
14. Garcia-Velasco JA, Mahutte NG, Corona J, Zuniga V, Giles J, Arici A, Pellicer A. Removal of endometriomas before in-vitro fertilization does not improve fertility outcomes: a matched, case-control study. *Fertil Steril* 2004; 81: 1194-7.
15. Virro MR, Larsen-Cook KL, Evenson DP. Sperm chromatin structure assay (SCCA) parameters are related to fertilization, blastocyst development, and ongoing pregnancy in in vitro fertilization and intracytoplasmic sperm injection cycles. *Fertil Steril* 2004; 81: 1289-95.