

# Even with Diminished Ovarian Reserve You Can Achieve Pregnancy

## Even with Diminished Ovarian Reserve You Can Achieve Pregnancy

### Diminished Ovarian Reserve: What Does it Means

The number of eggs and their quality are reduced at a given age. Women with diminished ovarian reserve have less eggs and more chromosomally abnormal eggs than women in the same age group. It reflects low response to fertility medications and more difficulty achieving a pregnancy. Women with diminished ovarian reserve may reach menopause one or more years earlier. As few eggs remain, still some of the eggs are chromosomally normal and pregnancy is very possible in women with diminished reserve.

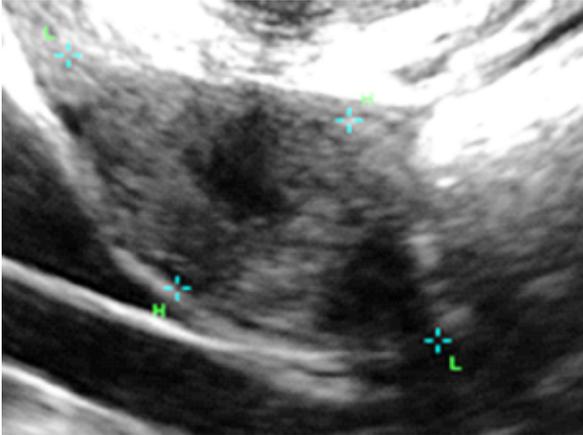
### Diminished Ovarian Reserve: How it is Diagnosed

**History:** Some historical factors may indicate low reserve including cigarette smoking, prior surgery of the ovary (removal of a cyst or an ovary), prior exposure to chemotherapy (particularly cyclophosphamide) or pelvic irradiation, early menopause in other family members (mother, sister), recurrent early first trimester pregnancy loss (indicating low egg quality) and others.

**Day 3 FSH:** It is an indirect marker for ovarian reserve. It is produced by the master gland in the brain. levels > 12mIU/mL indicates low reserve. It is less accurate than AMH or ultrasound.

**AMH:** is a protein produced by the cells surrounding the egg in

small size follicles. It is more accurate than day 3 FSH. Levels  $<1.5\text{ng/mL}$  indicates low reserve



Low antral follicle count  
(Ovarian Reserve)



Good antral follicle  
count (Ovarian  
Reserve)

**Vaginal Ultrasound:** in expert hands (a reproductive endocrinologist), it is an accurate measure for ovarian reserve. The number of small follicles  $<10\text{mm}$  especially on day 2-5 of menstrual cycle is an accurate indicator for ovarian reserve and response to fertility medication. The presence of an advanced follicle  $>13\text{mm}$  on day 2 or 3 is also an indicator for low reserve as it indicates that the ovary is under increased stimulation from FSH produced the master gland.

More details on ovarian reserve tests can be found [here](#).

## **Diminished Ovarian Reserve: What Should you Do**

If all other fertility factors (male factor, tubal factor..) are normal *you should attempt to conceive irrespective of ovarian reserve*. Ovarian reserve tests are not absolutely accurate. They do predict response to ovarian stimulation but are not very good in predicting pregnancy. Two general options exist: i. regular intercourse or ii. ovarian stimulation to produce more than one egg followed by IUI or IVF.

## **Diminished Ovarian Reserve: What Should your Reproductive Endocrinologist Do**

Your reproductive endocrinologist should ascertain ovarian reserve with multiple modalities: ultrasound and blood work. The infertility workup should be completed first: sperm analysis, hysterosalpingogram test for patency of fallopian tubes as well as preconception labs. Your infertility specialist should be able to advise you on the treatment protocol that is more likely to achieve a pregnancy. *Fertility specialist should not deny treatment to women based on diminished ovarian reserve*. Every woman with diminished reserve should be offered treatment at least once.

If the treatment plan involves ovarian stimulation, a special stimulation protocol or adjuvant treatment should be considered hopping at increasing the ovarian response (number eggs produced during the cycle). Some of the modifications commonly used are increasing the dose of gonadotropins, use of antagonist or flare antagonist, addition of clomid or letrozole, pretreatment with testosterone and use of growth hormone.

## **Diminished Ovarian Reserve: What would you expect from fertility treatment**

Well it depends on few factors: **Age and Relative Response to Fertility Medications**

If a younger women e.g <37 years produce two or three good quality embryos at the end of stimulation, they have a reasonable potential to achieve a pregnancy after IVF. The chance of getting pregnant in women older than 40 with few embryos is much lower. When one compare effects of low ovarian reserve and age on reproduction it is clears that age has more negative effect on reproduction than age. Age is associated with low egg quality while ovarian reserve mainly speak for the number of eggs in the ovary. *Younger women with low egg production fairs much better than older women with good reserve.*

Response to ovarian stimulation is not created equal. Women that produce four or more large follicles >15mm are at much better chance for pregnancy after IVF. On the other hand those that have lesser response <3 follicles are a much lower chance for success and should consider converting their cycle to IUI or just cancel the cycle if they have male or tubal factors. They then can try again after considering a modification of the stimulation protocol. In women that produce > 3 -4 eggs IVF is substantially more successful (about three times) than IUI.

Because the response to fertility medication is difficult to judge just based on ovarian reserve markers, most women should be encouraged to try ovarian stimulation once at least and most women should not be denied treatment based on the notion of low ovarian reserve.

---

## **Androgens: Improving Response**

# to Ovarian Stimulation prior to IVF

## **Androgens: Improving Response to Ovarian Stimulation prior to IVF**

Ovarian stimulation is the most significant improvement in IVF. Response to stimulation together with age are the most important determinants of successful outcome. Women with prior low response to stimulation and women with expected low response (diminished ovarian reserve) are at higher risk for cycle cancellation and produce a smaller number of mature eggs and embryos. Many approaches were suggested to improve response in low responders including

Increasing the dose of gonadotropins (injection medications)

Use of antagonist protocol

Use of flare lupron protocol

Use of oral medications e.g clomid or letrozole

Synchronization of follicles prior to stimulation using estrogens

Minimal stimulation IVF

Adjutant use of growth hormone

Use of androgens.

## **Androgen may Improve Ovarian response to stimulation**

Testosterone is known to increase the sensitivity of the ovary to FSH (the hormone that stimulate recruitment and development

of follicles in the ovary). Testosterone increases the number of FSH receptors in the follicle and thus its response to stimulation. Women that naturally have high androgens e.g polycystic ovary syndrome (PCOS) show a strong response to FSH. Androgen stimulation increases growth of early follicles and expands the number of follicles available for stimulation. Agonists (Lupron) and antagonists (Ganirelix) used in ovarian stimulation suppress testosterone levels in some women.

## **Androgen Preparations**

Two major preparations are available to deliver androgens prior to starting stimulation

Testosterone gel 10 to 12.5 mg applied to skin per day for 21 days or

DHEA oral tablets 75 mg for variable period 4 weeks to 4 months

### *Transdermal Testosterone*

There were three randomized clinical trials (generally the best type of studies in biological sciences) investigating the use of transdermal testosterone prior to IVF. Of the 221 patients included in these studies. Women receiving testosterone required less fertility medications, had significantly more eggs retrieved and less cycles were cancelled due to low response. There were no side effects in all studies. There was a two fold increase in pregnancy and live birth rates in women that used transdermal testosterone. *There is evidence that transdermal testosterone prior to stimulation improves IVF outcomes.*

### *Oral DHEA*

The mechanism of action of DHEA is not well understood. There were many studies on DHEA but only one was randomized clinical trial. When all the studies with control group were

considered, they demonstrated a significantly lower number of oocytes retrieved in DHEA treated women when compared to the controls. There was [no significant difference in the clinical pregnancy rate](#) between women pre-treated with DHEA compared to those without DHEA pre-treatment. It is possible that DHEA can improve embryo quality, but this did not translate into higher pregnancy rate. It is suggested that DHEA should be used for 2-4 months prior to IVF which delays treatment start.

The conclusions related to the use of androgens prior to IVF require more confirmation in larger studies. However, if androgens are used, transdermal testosterone is the preferred androgen pre-treatment prior to ovarian stimulation and IVF.

---

## [Thyroid Cancer and Future Fertility](#)

### Thyroid Cancer and Future Fertility



Thyroid Cancer and

Thyroid cancer is diagnosed in 45,000 individuals each year in the US. Its treatment may affect future fertility in men and women. It is more common in women with female to male ratio of 3 to 1. It is the most rapidly rising cancer in women living in the US. Thyroid cancers are commonly diagnosed in young women in their reproductive years. Treatment of thyroid cancer generally yields excellent results, with the majority of women surviving 10 years or more after diagnosis. Some women develop thyroid cancer due to iodine deficiency in diet or prior neck radiation. Some types of thyroid cancers are related to inheriting an abnormal gene.

Several types of thyroid cancer are recognized 1. Papillary cancer 2. Follicular cancer 3. Medullary cancer 4. Anaplastic cancer 5. Thyroid lymphoma. Papillary and follicular cancers are less invasive tumors and are encountered in the majority of women diagnosed with thyroid cancer. They also respond to estrogen as they carry estrogen receptors. Estrogen may promote growth of thyroid cancer cells. Thyroid cancers are usually suspected on neck examination followed by ultrasound or Iodine scan then biopsy. In general, treatment of thyroid cancer require total thyroidectomy-surgical removal of the thyroid gland followed by radioactive iodine to ablate any thyroid remnants. This is followed by long term thyroid hormone replacement. Long term follow up is required after treatment.

## **Effect of thyroid cancer treatment on the ovary**

Thyroidectomy followed by thyroid hormone replacement is not known to affect future fertility in men and women. Radioactive iodine can affect the number and quality of eggs remaining in the ovary. The effect is dependent on the dose of radioactive iodine and the age at treatment. Twenty to 30% of women

experience transient amenorrhea or irregular menses starting about 3 months after treatment. Normal menses resume about 6 months later. Permanent ovarian failure is rare but may occur in women at age 40 or older at the time of treatment. Increased incidence of miscarriage is reported in the first year after treatment. With the exception of miscarriages, there is no evidence that exposure to radioiodine affects the outcome of subsequent pregnancies and health of borne children.

## **Effects of radioactive iodine treatment on the testes**

Effect of radioactive iodine treatment may be more severe in men. and is related to the total dose of radioactive iodine received. Transient reduction in testosterone and sperm count may occur but sometimes permanent reduction in sperm count and testosterone levels. Men who received large total dose sometimes sustain permanent damage to the testes with absence of ejaculated sperm-azospermia. There is no evidence of effects of radioactive iodine on their newborn children, although its advised that men avoid fathering children for 6 months after treatment.

## **Options for fertility preservation**

Men interested in future fertility should consider sperm freezing prior to radioiodine treatment. Women should also consider fertility preservation if they will be treated with radioactive iodine and are older than 35 years. Radioiodine treatment will reduce their ovarian reserve. In addition they will be required to avoid pregnancy for a year or so. Options available for preservation of fertility in women include ovarian stimulation and egg retrieval followed by egg or embryo freezing. Ovarian stimulation can be modified to avoid estrogen exposure during stimulation. Moreover, in familial thyroid cancers, embryos can be genetically tested to avoid

transmission of the abnormal gene to children. Men and women diagnosed with thyroid cancer can benefit from consultation with a fertility preservation specialist prior to treatment to discuss effects on gonads and methods to preserve future fertility. Read more at <http://nycivf.org>

---

## **Ovarian Reserve Revisited-Do You Have Enough Good Eggs?**

### **Ovarian Reserve Revisited-Do You Have Enough Good Eggs?**

#### **Trying to conceive over age 35 is generally not easy**

I know because I tried for years to have a baby without success. While there are many factors which impact conception, one of the first concerns for women over 35 is if they have enough healthy eggs to get pregnant. Research has shown that women carry a reserve of eggs throughout their lives and that reserve diminishes over time. There are several tests which help to determine ovarian reserve including antral follicle testing, the clomid challenge and the AMH test which is relatively new.

#### **The antral follicle test**

Uses vaginal ultrasound to count and measure the small follicles, antral follicles, on the ovary. The higher the

number of antral follicles, the better ovarian reserve and better odds for conception.

## The AMH Test

Anti-mullerian hormone test, measures the levels of AMH in a woman's blood. Since this hormone remains relatively constant over the menstrual cycle, it can be tested at any point in the month. Women with higher AMH levels tend to have a better ovarian reserve and a better chance at conception.

## When I decided to try to conceive one last time at age 44

My [reproductive endocrinologist](#) began by ordering the *Clomid Challenge Test*. For the test, I took clomid, a fertility drug used to induce ovulation, for 5 days. Generally speaking, the procedure works like this:

- On Day 3 of your menstrual cycle, a blood test is given to measure your FSH, LH, and estradiol levels.
- On Day 5 of your cycle, you begin to take a 5-day supply of clomiphene citrate, 100 mg of clomiphene each day for five days.
- On Day 10, you will have another blood draw to check FSH, LH, and estradiol levels again.

Normal results include low FSH values on both Day 3 and Day 10, and low estradiol values on Day 3. Results are abnormal if your FSH values are elevated. Your doctor may decide to re-test if your results are abnormal.

My results were normal but that is a fraction of the total conception story and half of the ovarian reserve story. [Ovarian reserve](#) consists not only of the quantity of eggs but also the quality of eggs. Research tells us that while tests like the clomid challenge check for the quantity of

eggs, the quality of eggs is generally determined better by age. This is an unfortunate fact for those of us over 35.

According to Dr. James Toner in his paper "Ovarian Reserve, Female Age and the Chance for Successful Pregnancy", once women reach their mid thirties, specifically 37, their egg quantity begins to diminish at a faster rate. Toner also reports that even if egg quantity is good, chances of a viable pregnancy drop due to the diminishing quality of eggs as women age.

Based on the research, it is clear that the averages do not look promising for women over age 35 trying to have a baby. There is, however, other information to consider. Let's take a look at the bell curve. Basically, about 2/3 of the cases for a given situation fall in the fat part of the curve meaning that averages generally apply to most people. However, there are still one third of the people who fall outside of the fat part of the bell curve and averages do not generally apply to them. As you look at your individual situation, it is your lab work, anatomy and physiology that matter. I am a classic example of defying the odds. My ovarian reserve quantity was good but that wasn't what was preventing me from conceiving a child. It took many more tests to determine that a badly placed uterine tumor was most likely preventing implantation. At age 44, the research showed that an average woman in my situation had only a 3% chance of having a healthy baby. Yet, I was able to conceive in two of 4 IUI treatments and gave birth to a healthy little girl 9 months ago at the age of 45.

## **There are many components to conceiving a child**

Ovarian reserve is one of them. There are also many medical interventions to boost the odds of conception. Medical research provides us with excellent information about

infertility and age including work on ovarian reserve. While the research tells us that the odds of getting pregnant in late 30's and 40's diminishes, one needs to remember that each woman is unique and she needs to work with her doctor to explore all options in her quest for pregnancy.

✘ *About the Author: Deborah Lynn is the creator/owner of Over 35 New Moms and a former corporate vice president. She holds degrees in Education, Kinesiology and pursued doctoral study in Physiology. She spent over 17 years working in the corporate environment and now focuses her time on raising her daughter and helping other women over 35 in their journey to have a baby. For more information, visit The Resource Guide for Pregnancy over 40 at <http://www.selfgrowth.com>*

---

## **Should you Consider Fertility Assessment when you do not Intend to Get Pregnant Soon?**

### **Should you Consider Fertility Assessment when you do not Intend to Get Pregnant Soon?**

If you do not intend to become pregnant in the near future, do you need to assess your fertility? It is very possible that many women and men will be screened for relatively a small number of individuals that will show abnormalities. From the individual point of view, however, there are two distinct

potential benefits:

## **Detection of abnormalities related to fertility and reproduction:**



Screening for fertility problems

Ovary: Diminished ovarian reserve and anovulation

Fallopian Tubes: tubal block

Male factor: abnormal sperm analysis

Other factors: abnormalities of the uterus or cervix

## **Detection of abnormalities related to the safety of getting pregnant:**

Screening for genetic abnormalities: carrier screening

Screening for other medical disorders and infectious diseases

*The decision to consult with a reproductive endocrinologist to assess your fertility is individual. One would be more interested in fertility consultation in the presence of*

1. Known Fertility Issue: PCOS, absence of menses, endometriosis, fibroids, PID, abdominal surgery, prior chemotherapy for cancer or lupus

2. Risk factor for low fertility: 35 years or older and intend to delay pregnancy

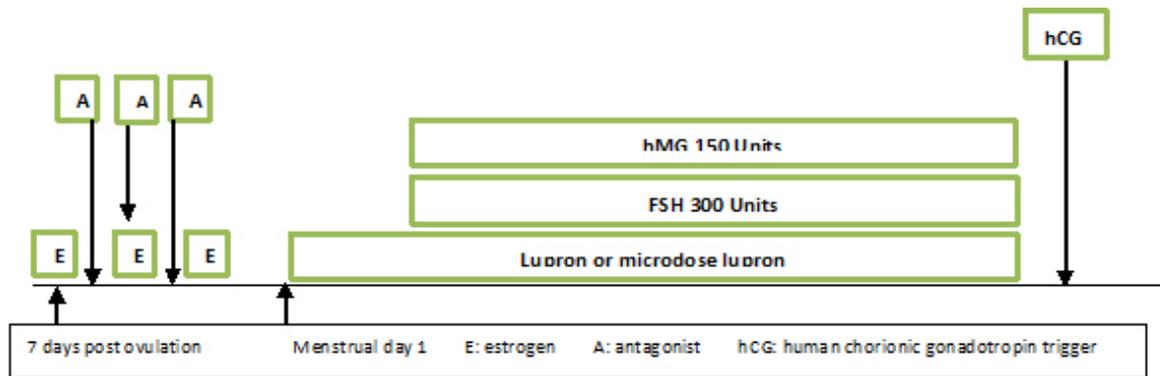
3. Genetic or medical risk factor: genetic screening especially in certain ethnic groups e.g Ashkenazi Jewish individuals

Informed about your fertility potential you may elect to either do nothing or respond to the abnormal results. If diagnosed with lower ovarian reserve you may elect to attempt pregnancy sooner or freeze your eggs. If a genetic abnormality is found in both partners you may consider testing of embryos to avoid transmission to the babies. If an abnormal sperm parameters were found, a referral to a urologist and / or sperm freezing could be considered.

There are no clear cut recommendation for fertility screening in men and women not intending pregnancy in the near future. Women intending to delay getting pregnant or with a known fertility issue and certain ethnic groups should consider screening for fertility and genetic problems.

---

## **Ovarian stimulation protocols for Low Responders prior to IVF**



Flare lupron protocol with luteal priming (synchronization) for Low Responders prior to IVF

## Ovarian Stimulation Protocols for Low Responders prior to IVF

Low response to controlled **ovarian stimulation** represent a significant fraction of [IVF](#) population presenting for fertility treatment. Low responders may represent 30% or more of women seeking IVF. The proportion may be larger in some areas due to delay in childbearing as a lifestyle choice. Low response to ovarian stimulation is commonly defined as producing 5 eggs or less after stimulation. While many factors may contribute to low response e.g smoking, prior surgery of the ovary, exposure to chemotherapy, the vast majority of are age related. Sometimes low response happens in younger women e.g 30 year old. Young low responders has a better chance of conceiving because their eggs, though few, are healthier (chromosomally normal) than older e.g >38 low responders.

Few strategies can increase egg yield and possibly egg quality in low responders, usually employing one or a combination of

- i. increasing the dose of gonadotropins,
- ii. avoiding long lupron suppression before start of

stimulation,

iii. adding an oral agent (clomid or letrozole),

iv. synchronizing follicles prior to start injections,

v. using androgen prior to cycle start and sometimes

vi. adding growth hormone.

There is no clear evidence to one protocol over the other. Increasing the dose above a total of 450 units per day does not seem to further increase egg yield in low responders. Some patients respond to one ovarian stimulation protocol over another. One example of low responder protocol is illustrated above. Estradiol and antagonist are used to synchronize the follicles before menses so that they are uniform in growth when stimulation starts. Short lupron is used (flare or microflare) to induce the release of internal gonadotropins. This is followed two days later by high dose of fertility medication (total 450 units per day).

There is some evidence that pre-treatment with androgens (testosterone) may improve egg yield. The evidence for the use of DHEA (dehydroepiandrosterone) is limited. There is also week evidence that the use of growth hormone may improve egg quality.

Embryological procedures are also sometimes suggested as [ICSI](#) of all available eggs to maximize fertilization and assisted hatching of the egg shell (zona pellucida). Pre-implantation genetic screening is unlikely to be helpful as few embryos are available for testing.