



Women with Older Ovaries



Prematurely Aging Ovaries Overview

Older women (generally above age 38), and younger women with so-called prematurely aging ovaries, will often find it harder to get pregnant. We, here at CHR, have a special interest in the “older women pregnancy and aging ovary” and have been conducting a lot of research on this topic. See [Ovarian Aging: is there a "Norm" in Contemporary ObGyn](#). Our program has become known in the community as the program of “last resort” and we, therefore, have probably proportionally more “older ovaries” under treatment than any other infertility center in New York City.

One of our patients, not too long ago, indeed, taught us a very important new lesson, which we, since, have diligently investigated with an increasing number of our patients. She, without our knowledge, had started taking the over the counter available, mild male hormone, DHEA and, as a consequence, greatly increased her oocyte (egg) yield in IVF. Indeed, after approximately four months of DHEA usage, her 43-year old ovaries behaved like those of woman in her 20ies.

Treatment Qualifications

If you are older than 40 and are unable to get pregnant after trying for six months, complete the [Prematurely Aging Ovaries Qualification Form](#) to determine if you qualify for our DHEA Treatment Program. This new treatment may improve the patients’ inherently limited pregnancy chances. Such a treatment offered itself when one of our patients, without our knowledge, started to take the mild male hormone, DHEA, and, subsequently, greatly increased her oocyte yield in IVF cycles. Indeed, this 43 year old woman, after approximately four months of DHEA treatment, featured ovaries which in function and sonographic appearance were indistinguishable from ovaries one would expect in much younger females.

Because of the extremely dramatic improvement in ovarian response by this patient after DHEA use, we felt ethically obliged to publicize this finding as quickly as possible since, in older women, time is, of course, of essence. A more [formal scientific report](#) of this case appeared in Fertility and Sterility, the official organ of the American Society for Reproductive Medicine (ASRM).

As we have emphasized from the beginning, one case in medicine may give hope but is certainly not enough to reach far reaching conclusions of any kind. We have emphasized this fact from day one; not only to our patients, but have also stressed it in our writings. At the same time we, however, have mounted a strong effort to investigate the use of DHEA as a potential extender of female fertility and have done so in two distinctive formats..

The ultimate study format for any clinical trial is the double blinded, prospectively randomized study. Such a study has been approved by our Institutional Review Board (IRB) and is under way. This study, however, mandates the use of a placebo, a sugar pill, in half of all patients. In practical terms this means that one half of all patients in this study will receive no treatment for up to four months. To give no treatment to an older woman who, maybe, has only a few months of reproductive life left, would not be considered ethical. We, therefore, had to restrict this study to a relatively young patient population, between the ages of 35 and 40 years. Women above age 40 will not be enrolled in this study.

They, however, are given the option of using DHEA, anyhow, by serving as their own controls. In this study, we compare patients' IVF outcomes, before they started using DHEA, to IVF cycle outcomes after the use of the medication. This form of a study is, of course, not as well controlled as a double blinded, prospectively randomized study, but, as this case so well demonstrates, such studies are not always possible in medicine and, sometimes, we have to accept a second best study format.

Two other IVF centers, one in New York and the other in Chicago, have joined us in the prospectively randomized study and we hope to be able to report results within a reasonably short time period. Finding infertility patients who agree to be randomized to possible placebo for four months is, of course, not always easy. We have, however, so far been able to place over 30 patients into the second study and are, therefore, already in a position to report further preliminary results. These results are currently being summarized for another formal scientific publication. However, because of the obvious time pressures involved in older women, we feel an ethical obligation to pass these preliminary results on as soon as we become aware of them.

Treatment Findings To Date - 10/20/05

At the annual meeting of the ASRM which took place between October 17-19 in Montreal, Canada. Drs Gleicher and Barad presented a number of research papers and, amongst them, the DHEA Update received considerable attention. This presentation by Dr. Gleicher offered the most recent update of CHR's DHEA data and also represented the first presentation of these data (except for CHR Grandrounds) on U.S. soil. Dr. Gleicher had presented earlier talks on the subject at the World Congress for IVF in Istanbul, at the ESHRE meeting in Copenhagen and on recent lecture tour through Japan and Taiwan. To a packed house, the presentation involved outcome data on DHEA patients who had completed IVF cycles and, for the first time, a life table analysis of all patients who had been started on DHEA which, therefore, also included the many spontaneous pregnancies we have witnessed in this patient population. This kind of analysis allows separating prognostic factors by such patient characteristics as age and, therefore, represents a very useful tool in counseling patients. What this analysis demonstrated is that women with prematurely aging ovaries, under age 38 years, have excellent pregnancy chances with the use of DHEA. Women with prematurely aging or physiologically aged ovaries, between ages 39 and 42 years also still have surprisingly good pregnancy rates, though lower than the former group. Above age 42, the establishment of pregnancy is difficult, even with DHEA, though our oldest ongoing pregnancy is in a patient who was age 45 years at time of conception.

Treatment Findings - 9/1/05

In this month's update we want to inform you about yet another remarkable observation we have made in patients who have started using DHEA: Spontaneous pregnancies, while patients wait to go into IVF cycles.

We are currently in the final stages of calculating what is called a life table analysis (LTA) for all patients who, over the last year, have been placed on DHEA. The purpose of such a LTA is to document all pregnancies that have occurred, whether spontaneously or through IVF, so that this overall rate can be compared to what would be expected from such a patient population.

Such a statistical comparison is not ideal because under best study conditions one would, of course, like to compare patients who were blindly given DHEA or a placebo. While such a placebo-controlled study is also underway, considering the patients who are candidates for DHEA treatment, we have encountered the expected difficulties in recruitment, since most, not surprisingly, do not want to take the risk of being blindly assigned to four to five months of placebo. We, therefore, have to work with the best evidence we are able to develop and that this, as of this time, the kind of LTA we are in the process of preparing.

While we have no final data yet available, our preliminary findings came as a surprise, even to us! We have seen so far, in addition, to the DHEA pregnancies with IVF, TWELVE (12) post-DHEA pregnancies in women who have not yet reached IVF treatment and approximately two third of these pregnancies are ongoing.

Considering who the patients are who we have placed on DHEA, these numbers are truly remarkable and exceed even our own, most optimistic expectations. We in principle recommend DHEA treatment only to two patient groups: The first group is older women, usually over age 42.5 years, with no prior IVF experience, or over age 40, if a prior IVF experience yielded only small numbers of good quality eggs/embryos. A second group is younger women, always under age 40, who have indisputable evidence of prematurely aging ovaries. Both of these patients groups, without treatment, have, as many studies in the literature have shown, only a minimal chance of spontaneous pregnancy. Indeed, most IVF programs will not even accept patients from either of these two groups because, even with IVF, their chances of conception are extremely poor.

In approximately 50 such patients, our data show that over 30% have so far conceived and over two-thirds of those who have conceived are either carrying ongoing pregnancies or have already delivered, if spontaneously conceived and pregnancies, conceived through IVF cycles, are added up.

As noted above, these preliminary numbers are truly remarkable and exceed even our own expectations. It is important to note that these numbers are preliminary! We will publish an "Update" on our website with final numbers as soon as those have become available. Because of the importance of this issue to so many women with aging ovaries, we want to make absolutely sure that our data are correct in their last detail and we are, therefore, currently re-reviewing the charts of all DHEA patients.

However, because time is of so much essence for women with aging ovaries, we have made it a policy to offer data to CHR's own patients, and to the readers of our website, as soon as reliable data become available to us. Research is slow and the publication of research data in scientific journals is even slower. As an example, the [report on our index patients](#), which led CHR into the research of DHEA over a year ago, will only now, in September, be published in Fertility & Sterility, the official organ of The American Society for Reproductive Medicine (ASRM). We are, however, planning on presenting the finalized LTA of our DHEA experience at the upcoming annual ASRM meeting in Montreal, Canada, which will take place in October. Our paper has been accepted for oral presentation for the first day of the meeting.

Treatment Findings - 8/12/05

For a number of reasons this month's update is quite remarkable and unusual: A first reason is that, once again, we can report on a very significant DHEA-related advance which was served to us on a platter by a patient. Most of you will recall that it was one of *our* patients at CHR who brought DHEA to our attention in the first place. This time, it wasn't even one of our own patients but a patient elsewhere who, through the internet, had become aware of our DHEA work and contacted us to tell us about her truly unique history. And in telling us, and documenting, her history in excruciating detail, she allowed us not only to correct her own presumptive diagnosis but, more importantly, provided us with convincing proof of the importance of DHEA for normal ovarian function and, possibly most importantly, may have pointed us into a direction which will allow us to understand, diagnose and treat the prematurely aging ovary better.

So what is this all about?

This patient, after a number of years of infertility, decided to investigate the medical literature to see what else she could do to better her obviously prematurely aging ovarian function with elevated, very abnormal FSH levels. Like our initial patient, she came across the one paper in the literature that suggested that DHEA may improve ovarian function to a small degree. She took this, however, a step further and asked her medical endocrinologist to investigate her adrenal glands, which produces DHEA. And, low and behold, this testing revealed that she, indeed, had very low DHEA levels in conjunction with certain other low sex hormones. Her medical endocrinologist correctly concluded that she, most likely, suffered from an adrenal enzyme defect which blocked the normal production of DHEA in her adrenal glands and prescribed DHEA substitution.

Even though this medical endocrinologist was apparently wrong in the exact enzyme defect he had diagnosed (that defect actually results in elevated DHEA levels), her treatment with DHEA, indeed, corrected, as was well documented, all of her hormonal abnormalities. Her DHEA returned to normal levels and so did her production of other hormones which are produced from DHEA, such as estradiol. In addition, in her first IVF cycle, after approximately 6 months of DHEA substitution, she produced more eggs and better eggs and embryos than in prior IVF cycles, conceived a triplet pregnancy and delivered, at age 39, a healthy son after six years of prior unsuccessful attempts.

So what does all of this mean?

First and foremost this patient is an experiment of nature which suggests that low DHEA levels may, indeed, be cause for infertility and, possibly, premature ovarian aging and that DHEA substitution may reverse some of these effects successfully.

In demonstrating these facts, this patient provides confirmation for our DHEA work which has suggested that DHEA substitution in older ovaries increases egg yield and egg as well as embryo quality. Since DHEA levels are known to decrease significantly with advancing age, the aging ovary can be seen as akin to that of a DHEA deprived ovary, where the cause of that deprivation, as in this patient, appears not age-related but due to an adrenal defect. In other words, this patient confirms that DHEA deprivation, if corrected, improves ovarian function. In doing so, this case validates the treatment of aging ovaries with DHEA.

Maybe more importantly, however, this case also may point towards a better understanding of the prematurely aging ovary and here is why: approximately 10% of women suffer from prematurely aging ovaries. They usually reach menopause prematurely and this condition is familial; i.e., it means that if your mother had early menopause, you, as her daughter, are at significantly increased risk for early

menopause, as well. The diagnosis of prematurely aging ovaries is, as we have repeatedly described in these pages, at times difficult to make, requires a high level of suspicion and, at times, cannot be made without taking patients into an IVF cycle. It is, therefore, no surprise that many women with this diagnosis go undiagnosed for long periods and are frequently misdiagnosed as so-called “unexplained infertility.”

All of this applied to this patient. She went undiagnosed for years. Only after her FSH levels became significantly abnormal was the problem recognized. And with great likelihood, will she experience early menopause, though she is currently attempting another pregnancy. This patient was, however, unique in one aspect: she was diagnosed with an adrenal enzyme deficiency which prevented the normal conversion of precursor hormones into DHEA.

This, of course, immediately raised in our minds the question whether there might not be other patients, like her? Indeed, one could speculate that this kind of an adrenal enzyme defect may be quite frequent. Many patients then could be expected to have, as a consequence of such a defect, low DHEA levels and these adrenal enzyme defects may, then, indeed, represent a significant cause for the premature aging of ovaries. In other words, the prematurely aging ovary may be an adrenal disease!

Such a finding would, of course, have huge significance for our field because it would give us, for the first time, tools to diagnose women with this condition early and then treat them correctly. Moreover, DHEA substitution may also allow us to delay their premature menopause.

We are looking for volunteers:

However, one swallow does not make spring, yet! We have a lot of work to do to confirm this very exciting theory and have, therefore, already instigated a study of young women with proven prematurely aging ovaries. In order to have very clear study criteria for our patients with prematurely aging ovaries, we have set strict criteria for patient selection for this study.

If you want to participate in this study, you have to be under the age of 35 and you have to have had an elevated FSH level on at least one occasion. If you believe that you qualify, please complete the [Prematurely Aging Ovaries Qualification Form](#).

Once confirmed to qualify for the study, you will be asked to spend a few hours at our Center on either the 2nd or the 3rd day of your menstrual period, at which time you will undergo a so-called ACTH stimulation test. This is a routine test for adrenal function.

What it means is that you will have some baseline bloods drawn; then you have a small amount of the hormone ACTH injected intravenously, followed by two more blood draws at 30 and 60 minutes after injection. How several of your hormones respond to the injection of ACTH, defines your adrenal function.

Treatment Findings - 6/27/05

Because women who potentially can expect benefits from DHEA treatment are usually at an age, and on a time-line, that do not allow for delays, we have made it a practice to publish on our website periodic updates on CHR's DHEA experience, as the data become available.

CHR is, of course, pursuing in parallel the scientific publication of these data; however, the scientific publication process is very slow and many patients do not have the time left to wait for such formal

publications. For example, the first report on the CHR's index patient, who gave us the idea to pursue the investigation of DHEA, over a year and a half ago, [appeared in print](#) in *Fertility & Sterility*, the official organ of the American Society for Reproductive Medicine (ASRM) in its September 2005 issue. Another manuscript, describing CHR's DHEA experience over the first year of treatment, will be submitted for publication soon.

In addition, we are presenting our DHEA data on an ongoing basis at international scientific meetings. For example, Norbert Gleicher MD, our Medical Director, presented updated DHEA data at the invitation of the organizers at the World Congress for ART in Istanbul, Turkey in May, and, just recently in June, at the Annual Meeting of the European fertility Society (ESHRE) in Copenhagen, Denmark. At both of these meetings the data received disproportionate attention from the community of fertility specialists. To keep the local New York Ob/Gyn community informed, David Bard, MD, presented the data at one of CHR's Grandround events in June.

The following is a summary of conclusions about CHR's DHEA data, as we presented them at these events, and as we understand them to be reflected by the clinical experience we have witnessed so far in our patients:

>>DHEA increases in older women oocyte numbers to a statistically very significant degree.

>> DHEA also increases egg and embryo quality in older women to a statistically very significant way.

>> DHEA appears to increase pregnancy rates with IVF in older women; however, while we are observing a very strong trend towards significance for this finding, the data have not yet reached statistical significance.

>> We have observed preliminary evidence, which has not reached statistical significance, and needs to be viewed with extreme caution, that DHEA may reduce the degree of chromosomal abnormalities in eggs and embryos of older women.

We are, therefore, to day in a position where we can state with considerable conviction that *treatment with DHEA benefits older women, as reflected by their IVF- cycle outcomes.*

We have also considerable evidence, though not as much as in older women, that *DHEA treatment has a similarly beneficial effect on younger women with prematurely aging ovaries.*

>> We also confirmed the initial observation in our index patient that the effectiveness of DHEA usage peaks after approximately 4 months of use.

>> Moreover, we strongly suspect (though do not yet have absolute proof) that co-treatment with gonadotropins further amplifies the positive DHEA effect on the aging ovary.

The conclusions we report here are based on what is called *observational* studies. The quality of results obtained from such studies is not equal to results obtained from *prospectively randomized* and *blinded* studies. We have, indeed, instigated such a study protocol for DHEA; however, because it involves the randomization of patients to placebo we have experienced considerable recruitment

problems into the study since patients with “older” ovaries are usually hesitant to take the risks of prolonged placebo treatments.

Our observational study is, however, of rather high quality because it involves patients *pre-* and *post-* DHEA treatment in unselected fashion and, indeed, also involves by now a large enough number of patients who serve as their own controls in that they, themselves, underwent pre- and post- DHEA cycles.

Finally, we are extremely confident of our data because, even, when we statistically corrected for the increased egg numbers, we observe after DHEA treatment, we still maintain high significance for improved egg and embryo quality.

We are on purpose not publishing our DHEA treatment protocols because we want to discourage self-treatment with DHEA. We, however, encourage colleagues to [contact us](#) with questions and will, on such occasion, gladly share our clinical experiences in more detail and describe our treatment protocols.

Patients who wish to consider treatment through CHR should [contact us](#) for a consultation for an appointment. Patients who live outside of the United States may request an appointment for a telephone consultation with a CHR physician. CHR is routinely cooperating on patient care with physicians from all over the world.

Treatment Findings - 5/19/05

The happy mother of a newborn 8lbs., 2oz. boy was 41 years old at time of her successful IVF cycle in July of 2004 which had been preceded by seven weeks of DHEA treatment. A prior IVF attempt in June of 2004 had to be cancelled after lack of ovarian response to ovarian stimulations. With identical ovarian stimulations and the DHEA treatment, we were able to produce 8 oocytes and 4 embryos, respectively. To date, five women waiting to go into IVF cycles have conceived spontaneously.

Previous Treatment - 5/05

DHEA not only increases egg numbers but also appears to improve egg/embryo quality. Our experience with DHEA has now reached 45 women with previously diagnosed impaired ovarian reserve. They have used the medication for various time intervals at a range from 4 to 48 weeks before starting an IVF cycle. Based on these patients we are so far able to compare 43 IVF cycles *before* with 33 cycles conducted *after* DHEA start. The following findings were noted:

- *Baseline FSH and ESTRADIOL levels did not change with treatment*
- *Egg production increased significantly from an average of 4.4 to an average of 8.6 oocytes (confirming further our previously reported update data*
- *Eggs after DHEA treatment produced high quality embryos at a significantly higher rate than eggs prior to treatment (35% vs. 16%).*

This latter observation provides the first evidence ever reported that DHEA treatment not only increases egg quantity but apparently also improves egg quality. If further investigations should confirm these early and, therefore, preliminary data, then DHEA could truly be seen as an “ovarian rejuvenator” by beneficially affecting two of the classical signs of ovarian aging, poor egg numbers and poor egg quality. Anecdotally, such an interpretation of these data is further supported by our

observation of a small number of totally unexpected spontaneous pregnancies in women with clear evidence of diminished ovarian reserve after they started DHEA supplementation.

Previous Treatment Findings - 3/05

Our experience with these over 30 patients, therefore, suggests the following:

- In women, ages 40 to approximately 44, DHEA, indeed, appears to increase oocyte yield. This increase is not observed in all women but in a horizontal assessment it is significant for the whole group studied.
- The data is not yet adequate to assess the value of DHEA in younger women, with evidence of prematurely aging ovaries, but preliminary trends suggest that DHEA may have similar benefits in these patients.
- We confirmed that the benefit of DHEA increases with time of use and peaks after approximately 4 months of use. Whether the plateau reached after 4 months DHEA use is time limited, and, if so, for how long before a decline is observed, is unknown.
- DHEA appears to enhance spontaneous fecundity/fertility. We make this statement based on the observation that, in this very unfavorable group of patients, 4 (!) conceived spontaneously while on DHEA treatment and waiting to enter an IVF cycle. This is, of course, anecdotal evidence in view of the small numbers; however, our expectation for spontaneous pregnancies in these patients is extremely low.
- DHEA use probably lowers baseline FSH levels. We cannot make this statement with absolute certainty because only one, out of two, statistical analyses performed on these data showed statistical significance so far.
- We do not know yet whether, in addition to oocyte quantity, DHEA also effects oocyte quality.

Next Step

The first step is easy, simply complete the [Prematurely Aging Ovaries Qualification Form](#) to determine if you qualify for our DHEA Treatment Program.