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Case Report

Treatment of sperm with the Protein Digestive Enzyme Chymotrypsin Markedly Improves Sperm Rapid Linear Motion of Sperm Pre and Post Wash Allowing a Live Delivery Following Intrauterine Insemination in A Woman with Marked Diminished oocyte Reserve

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Abstract:

Patients with sperm with the absence of sperm with rapid linear motion (RLM) after processing for intrauterine insemination (IUI) have a very poor pregnancy rate. A couple with 6 years of infertility with the female partner having a very diminished oocyte reserve (DOR) as evidenced by an undetected antimullerain hormone level was complicated by the male partner having the absence of sperm with RLM both before and after sperm wash prior to IUI. Treating the sperm before sperm wash with the protein digestive enzyme chymotrypsin not only markedly improved the RLM of the post washed sperm but resulted in a live delivery after just one IUI with enzyme treated sperm. This supports the hypothesis that at least in some cases a toxic protein possibly added as sperm traverses the ejaculatory ducts may adversely affect quality of sperm motility which can be negated by protein enzymatic neutralization of this possible toxic protein.

Key words: rapid linear motion; post-washed sperm; chymotrypsin, intrauterine insemination; diminished oocyte reserve

Introduction

A previous study found that in 1448 couples where intrauterine insemination was performed 383 (26.4%) found no sperm with rapid linear motion (RLM) (1). There were 80 sperm specimens that did not demonstrate any sperm with RLM even in the final washed specimen used for IUI. There were some pregnancies but a low percentage (2 of 80, 2.5%) [1].

Pregnancy rates are also very low following an IUI with sperm laden with anti-sperm antibodies [2,3]. An antibody is a protein. Pregnancies are extremely rare following IUI with sperm with a functional impairment of the sperm membrane probably related to a toxic protein added as the sperm traverses the ejaculatory ducts which is measured by a hypoosmotic swelling test (HOST) [4,5]. A marked improvement in success rates in achieving pregnancies following IUI with sperm laden with anti-sperm antibodies or low HOST scores have been achieved by first treating the sperm before washing with the protein digestive enzyme chymotrypsin [6-8].

The possibility exists that in some instances the presence of a toxic protein is an etiologic factor in adversely effecting RLM both pre and post wash. Reported here is the first case of pretreating sperm without RLM with chymotrypsin resulting not only in marked improvement of sperm with RLM but also a successful pregnancy following IUI in a woman with marked diminished oocyte reserve (DOR).

Case Report

A 35-year-old woman presented with 6 years of primary infertility. Her serum anti-mullerian hormone level (AMH) level was 0.55 ng/ml 3 years before her initial visit to our infertility center. She was advised by her reproductive endocrinologist/infertility physician at that time since she had DOR related to her low serum AMH she should immediately try in vitro fertilization embryo transfer (IVF-ET). Unfortunately, the IVF oocyte retrieval failed to obtain any oocytes. Thus, the physician did not want to try IVF-ET anymore but did 5 IUI's in natural cycles without any progesterone (P) supplementation in the luteal phase.

For the 2 years prior to her first visit to our infertility center she merely tried intercourse without monitoring. When she was first evaluated in our practice her menses were still regular, but her serum AMH was now markedly low at less than 0.015ng/ml (thus undetectable).

Her 38-year-old husband had a semen analysis the day of her 1st IUI in our practice. The results are seen in Table 1.

	Pre-wash	Post-wash
Concentration	17.4x10 ^{6} /ml	3.47x10 ^{6}/ml
Percent Motility	67.6%	74%
Percent RLM	0%	0%
Percent slow or non-linear	56.3%	90%
Percent non-progressive motility	6.3%	10%

Table 1: Semen analysis on day of first IUI pre and post wash

Since the woman had regular cycles and did attain the criteria of a mature dominant follicle, i.e., an average diameter between 18-24mm and serum estradiol (E2) of at least 200 pg/ml, she was not given any follicle maturing drugs [9,10]. She was treated with P vaginal suppositories 400mg twice daily in the luteal phase [11]. She did not conceive that cycle with an IUI performed with sperm post-wash with 90% slow or non-linear motility but 0% with RLM. Her serum FSH that cycle was only moderately elevated at 15.2 mIU/ml and the serum E2 was 25 pg/ml. (Table 1)

In cycle 2, the serum FSH was 20.2 mIU/ml with a serum E2 of 28 pg/ml on cycle day 2. For this cycle we evaluated for the first time whether pre-treatment with chymotrypsin could provide some sperm with RLM post-wash in a patient failing to demonstrate sperm with RLM post-wash in a previous cycle. The results are seen in table 2.

	Pre-wash	Post-wash
Concentration	10.3x10 ^{6} /ml	10.5 x10 ^{6}/ml
Percent Motility	62.1%	76.3%
Percent RLM	0%	15%
Percent slow or non-linear	90%	80%
Percent non-progressive motility	10%	5%

Table 2: Semen parameters before and after sperm wash in second cycle of IUI with pre-treatment of sperm with chymotrypsin prior to sperm wash.

There was a marked improvement of sperm with RLM (15%). She was given an increase in the dosage of P suppositories in the luteal phase from 800mg to 1200mg because in her first cycle she failed to attain a homogeneous hyperechogenic pattern in her mid-luteal phase by transvaginal pelvic sonography [12]. She conceived that cycle and had a full-term healthy baby.

She had been treated in both cycles 1 and 2 with cabergoline 0.5mg twice per week and she received 1 mg leuprolide acetate at mid-luteal phase (explanation on reason will be mentioned in discussion section).

Discussion

The possibility exists that marked improvement of the percentage of sperm with RLM after chymotrypsin may have occurred even had the enzymatic treatment not be given. However, we have vast experience even since our publication of 75 sperm specimen with zero% RLM prepared for IVF and 383 sperm specimens prepared for IUI with no sperm with RLM post wash [1]. We have never found such a marked improvement in the percent of RLM without the use of chymotrypsin pre-treatment. The hypothesis of mechanism of action is that the protein digestive enzyme negates the effect of some toxic protein in the semen that markedly adversely effects quality of motility.

We are presently prospectively evaluating a series of evaluating the effect of chymotrypsin on improving RLM of sperm with no RLM post wash, but this may take a while since this is not a common occurrence. Hopefully this case report will stimulate other physicians treating infertility to evaluate chymotrypsin for poor post wash quality of motility and report their outcome to determine whether this beneficial effect is not going to be helpful for the majority of similar cases (thus suggesting another cause other than a toxic protein) or hopefully find that this

treatment has great efficacy for the majority of zero% post wash sperm with RLM. We plan on evaluating chymotrypsin pre-treatment not just on whether it can improve post-wash quality of motility but how this translates into live delivered pregnancy rates.

Though this patient was advised by several other infertility consultants that a live delivery would be highly unlikely related to such a low serum AMH level, we were not surprised because we have seen a large number of women who had successful pregnancies in natural cycles not only with extremely low egg reserve, but even women who appeared to be in overt menopause [13-15]. We believe that to maximize success one should follow the tenets of the FSH receptor up-regulation technique [16]. One of the tenets of this technique is to not use follicle stimulating drugs when the serum FSH is already elevated to prevent down regulation of FSH receptors that may be also responsible for the production of an enzyme or

cytokine needed for successful embryo implantation. In cases like the one described, the FSH receptor up regulation technique avoids any drugs that raise serum FSH as long as the patient obtains a mature dominant follicle in natural cycles [16]. Sometimes a small boost of FSH may be given to attain a mature dominant follicle in the mid to late luteal phase when the FSH has decreased related to the rising E2 levels if the woman luteinizes before full follicular maturation was achieved [16].

Infertile women over age 30, but even younger ones with significant dysmenorrhea (as seen in the patient described), frequently have more inflammation than normal and thus require more P in the luteal phase to secrete higher levels of immunomodulatory proteins e.g., the progesterone induced blocking factor (PIBF), to neutralize excessive cellular immune reaction above the normal needed for autoimmune remodeling of thick-walled uterine arteries in the proliferative phase to allow creation of some thin-walled spiral arteries needed to allow nutrient exchange between mother and fetus [9,11, 17-19].

There is evidence that the autoimmune remodeling of thick-walled uterine arteries is facilitated by the effect of P in blocking dopamine. One of the reasons for blocking dopamine is to increase cellular permeability thus allowing infiltration into pelvic tissue of irritants creating an increased proliferation of cellular immune cells (especially natural killer cells) [17]. Thus, drugs that release dopamine from sympathetic nerve fibers may inhibit excessive cellular immune reactions and thus prevent rejection of the fetal semi-allograft [20-24].

Another dopaminergic drug that can inhibit symptoms of the increased cellular permeability syndrome e.g., pelvic pain, headaches, fibromyalgia, and carpel tunnel syndrome is cabergoline [25-27]. In the case of the patient reported here, she was treated with cabergoline instead of dextroamphetamine because there are a few states in the United States e.g., New Jersey, where she resides, which precludes prescribing class II drugs off-label. There is evidence that most cases of DOR are related to increased cellular permeability with inflammatory damage of the ovaries which is frequently associated with various types of pelvic pain [20]. However, sometimes DOR related to excessive inflammation may not be associated with pelvic pain but other manifestations of the increased cellular permeability syndrome e.g., ulcerative colitis and sometimes with no symptoms at all [22-24]. One cannot say for sure, however, that a successful pregnancy required the use of cabergoline for this accomplishment.

Similarly, we cannot state with certainty that the mid-luteal phase injection of 1mg leuprolide acetate was needed to achieve the pregnancy, but we have some data that it can improve implantation rates in women with normal egg reserve or DOR [28].

Conclusion

The novel aspect of this review is that this may be the first case of treating sperm with zero% RLM even after washing with the protein digestive enzyme chymotrypsin and not only achieving sperm with very good RLM but resulting in a live delivery without resorting to in vitro fertilization embryo transfer (IVF-ET) with intracytoplasmic sperm injection (ICSI). These manuscripts are some studies in the literature or in using certain methods of improving sperm motility e.g., marked improvement in RLM after zero% post-wash without pentoxifylline or other activation. I am reasonably sure that there are no case reports or studies on the use of chymotrypsin to cause such an improvement. There are several case reports in the literature showing live deliveries even when serum AMH is undetected including a recent one involving natural conception in a 46.5-year-old woman in overt menopause [15]. However, several recent reviews concerning DOR with multiple references do not even mention the FSH receptor techniques and the importance of not raising serum FSH using higher dosages of FSH [29-32]. Thus, another purpose of this manuscript is to familiarize the readers with this concept for trying to correct infertility in women with marked DOR.

Limitations

1. We cannot prove that the chymotrypsin treatment was definitely the reason for the marked improvement in RLM-it could have just been fortuitous. We will try it on other patients and hopefully some of the readers will try it and report their results. The enzymatic therapy may have been responsible in this case, but it could turn out that the hypothetical toxic protein only occurs in a minority of cases and thus the technique will not be successful in the majority of similar circumstances.

2. Though this case is another example of the fact that women with extremely low egg reserve even with undetectable serum AMH can achieve a live delivery even without IVF by supplementing in the early luteal phase with P and treating with dopaminergic drugs to counteract potential excessive cellular immunity and rejection of the fetus, and even mid luteal phase injection of leuprolide, it is also possible that only some of these treatments were needed to achieve this pregnancy. It is even possible that the only thing that was needed was to improve quality of motility and do the IUI.

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