The below questions were given to Judy Norsigian by Lynne Millican, and Judy passed the questions along to the Dept. of Health and Human Services, and their response is included below:

Judy;
Here's some of my thoughts and questions. Most of these pertain to lupron. Hope that you'll be able to forward some answers or responses, and also maybe garner some interest in this issue. Thanks and good luck!

- Is it an accurate statement, quoting printed materials, that "none of these medications (pergonal, clomid, lupron) have been shown to be harmful"?

- Regarding a Journal of Assisted Reproduction and Genetics article (Vol.9, No.3, 1992; p.256) which states: "Whether different types of hormonal stimulation have different effects on the nuclear oocyte quality is not yet clear" ... is there now clarity on whether different types of hormonal stimulation have different effects on the nuclear oocyte quality?

- Are there any large scale studies underway to study the effects of fertility drugs (pergonal, clomid, lupron) on women and children?

- "The rate of development of embryos obtained during down-regulated cycles was significantly higher than that of embryos developing in conventional stimulation cycles ... it is suggested that (these) embryos should be cryopreserved earlier to correct for their accelerated development" (Fertility & Sterility, Vol.55, No.4, April 1991; p.792): What is responsible for this accelerated development, are there any longterm effects from such acceleration, and what percentage of GnRHa produced embryos are being cryopreserved prior to transfer?

- Have there been any pituitary function tests done on women either before or after treatment with lupron; and if so, were there any findings?

- If the human body only makes LH and FSH, how would human receptors bind to an analog of GnRH?

- How can a peptide (lupron) be inhaled, as in the "lupron nasal spray"? And how can the injectable lupron peptide be presevered in benzyl alcohol, which is destructive to peptides?

- Given that lupron is a pregnancy category X drug, causes fetal abnormalities in 1/600th the human dose, and chromosomal abnormality and dwarfism have been reported - why is this drug being used in fertility treatment?

- What is the etiology of the memory loss associated with use of lupron?

According to 'Neuropsychologic Dysfunction in women following leuprolide acetate induction of hypoestrogenism' in the Journal of Assisted Reproduction and Genetics (Vol.10, No. 1, 1993; p.53), "a significant proportion of women, more than half in some cases, showed significantly worse performance on one or more memory tests while on lupron. When memory tests performances

were combined, a substantial majority of the patients showed difficulty with memory while on lupron. Slightly more than half of the patients showed decline (on test of fine motor coordination). Another article, 'Adverse effects of leuprolide acetate depot treatment[5] in Fertility & Sterility (Vol.59, No.2, February 1993, p.448), states "Although the mechanisms of these symptoms are unclear, GnRH-a treatment should be discontinued if depression or short-term memory loss develops". What implications do these facts have? If more than half of the patients suffered memory loss, then more than half should not have been receiving the drug: how then can it be prescribed for nearly all IVF cycles?

- In women treated with 6 months of lupron, 13% bone loss is reported, and 11% of that loss reverts within 12 months post treatment. What explains for the lack of 100% return of pre-treatment bone density levels? And is there any data on bone density status in lupron treated women beyond the first year post-trearnent?

- Were there any dosing studies conducted to determine the lupron dose in treatment of infertility, endometriosis, fibroids, PMS? Upon what basis is the dosing determined for administration to women in all approved and unapproved use?

- What is the purpose of the various needles used in lupron administration, given that the bevel of the needle is the same, and a typical dose of 10 units on an insulin syringe is also calibrated on the 'lupron syringe'? If nasal spray is available, why use needles at all?

- How can children tolerate 7.5 mg lupron depot injections indefinitely for treatment of precocious puberty, yet adult women are prescribed 3.75 mg. and are not to exceed *6* months of treatment?

- Women are being told by their physician that their symptom, complaint and/or diagnosis is not related to lupron use, while the FDA's spontaneous reporting system and the PDR acknowledge these very symptoms, complaints, and diagnosis as ‘lupron adverse reactions’. If a connection is denied by the physician, isn’t is illogical to assume the physician is reporting these symptoms, complaints, and diagnosis to the FDA?

- The abortifacient usefullness of GnRHa has been previously evaluated (Fertility & Sterility, Vol. 59, No.2, February 1993; p.446). What is the current status of lupron being prescribed for the unapproved use in abortion?

- The study used to gain the initial approval for lupron in male prostatic cancer consisted only of patients with stage "D" prostate cancer - meaning metastatic cancer, which often involves the bone. Yet it is known lupron has an effect on the bone. There is bone involvement with the men ("metastatic CA") and there is bone involvement with the women ("osteoporosis"). What data exists to indicate that it is not the drug itself?

Thanks,

Lynne

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

**Food and Drug Administration -
RockvilleMD 20857**

January 26, 1995

Judy Norsigian
Boston Women's Health Book Collective
240a Elm Street
Somerville, MA 02144

Dear Judy,

I have had an opportunity to look through the list of concerns re: infertility treatments that you gave me at the last CONRAD TAC meeting. I hope these responses will be helpful.

Concern: "Is it an accurate statement, quoting printed materials, that 'none of these medications (pergonal, clomid, lupron) have been shown to be harmful'?"

Comment: These medications have both benefits and risks. Here I would refer to the PDR ("prescribing information") for the specific drugs. Risks are discussed.

Concern: Questions re: hormonal effects on nuclear oocyte quality.

Comment: This appears to be a theoretical question posed by the authors of the Journal article. There is no evidence presented to date that different effects exist.

Concern: "Are there any large scale studies underway to study the effects . .

Comment: Re: the drug approval process, studies were done to establish effectiveness and safety (as labeled) for the approved indications. Epidemiological evaluations continue to look for subsequent benefit/risk assessments. Whether pharmaceutical companies are conducting studies under the IND process is not releasable information.

Concern: "The rate of development of embryos obtained . . . "

Comment: The accelerated development observed could have many explanations. Possibly the authors of the Fertility and Sterility article have suggested some mechanisms. This observation might also be described as the rate of development being significantly lower in embryos developed in conventional stimulation cycles. Re: long term effects and percentage questions, again I would have to refer to the authors or further literature search.

Concern: "Have there been any pituitary function tests done on women either before or after treatment with lupron; and If so, were there any finding?"

Comment: Here I can only speak to Lupron for Its approved Indication In women-management of endometrlosls. Studies Included pituitary testing In the form of LH and FSH monitoring. The expected effects were observed In that Lupron use Initially produces a "flare" of LH and FSH production followed by a down-regulation (very low levels). Once medication Is stopped, these pituitary hormones return to normal patterns of secretion.

Concern: "If the body only makes LH and FSH, how would human receptors bind to an analog of GnRH?"

Comment: Gonadotropln releasing hormone (GnRH) Is a hypothalamlc factor made by the human. It Is usually secreted In a pulsatile fashion and controls the pituitary release of FSH and LH. The GnRH analog binds to the receptors at the pituitary level overriding the natural GnRH.

Concern: "How can a peptlde be Inhaled . . .?"

Comment: Medications can often be formulated for several routes of administration (IV, IM, subcutaneous, Inhalation, nasal, oral, etc.). Here I would refer to the prescribing Information (PDR) for Nafarelln (the Syntex nasal spray also called "Synarel") for actual content of the spray (It does not contain benzyl alcohol).

Concern: Given that lupron Is a pregnancy category X drug, . . ."

Comment: Category X Is often used when there Is no conceivable Indication for the drug to be used during pregnancy. Even for lupron use In Infertility treatment (which Is not currently approved), It would be used prior to conception.

Concern: What Is the etiology of the memory loss associated with lupron?

Comment: As for all the nervous system disorders reported with lupron. and other GnRH analog use, this Is most likely related to the state of hypoestrogemsm. These same phenomena have been observed In other hypoestrogenic states (for example In some cases in the postmenopausal period).

Concern: " . . . how can it be prescribed for nearly all IVF cycles?"

Comment: I do not know If lupron Is prescribed for "nearly all IVF cycles" and It Is not Indicated for this use. Re: the memory loss and other performance tests, these were tested In women using the drug for longer term Indications. I have not seen results for IVF type use.

Concern: "What explains for the lack of *100%* return of pre-treatment bone density levels? . . . "

Comment: Hypoestrogenemia is associated with a loss of bone density. Return to normal estrogen levels does not guarantee return to previous bone density. This is similar to the state of bone loss issues in the post menopausal period. I would have to do a literature search, but am not aware of bone studies beyond a year post-treatment.

Concern: Dosing studies

Comment: Dose ranging studies and/or justification is required as part of the approval process for a new drug or new indication. Lupron is approved for the management of endometriosis. The dose was based on an evaluation of the amount needed to suppress LH/FSH (and thus estrogen) levels.

Concern: purpose for various needles, etc.

Comment: As far as we are aware, needles and syringes are only supplied specifically by the sponsor for Lupron depot-ped intended for pediatric use. As you can see from the labeling, any needle (usually 22 gauge) can be used as well as any appropriate syringe.

Nasal spray is available from Syntex as Nafarelin and is

used twice a day. Whether injections or nasal spray is used is up to the provider and client.

Concern: Use in children questions

Comment: The use in treating inappropriate GnRH secretion in children with central precocious puberty is very different than the use in normal adult women. Children with precocious puberty have an abnormally high level (and abnormally timed secretion) of GnRH to be countered. Use in adult women involves countering a normal secretion.

Regarding bone loss, it is thought that women lose bone due to estrogen deficiency. Estrogen is not a factor for bone loss in pre-pubertal children (they normally have low levels of estrogen).

Concern: Adverse reactions concerns.

Comment: Lupron labeling contains discussion of adverse reactions. Most of these were discovered during the clinical trials. Any reactions outside these already reported (or otherwise unusual) should certainly be submitted.

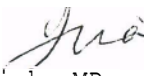
Concern: Abortifacient questions

Comment: I have no information re: the use of lupron for abortion.

Concern: Questions re: bone.

Comment: Certainly GnRH agonists create an estrogen deficiency state in women which is related to bone mineral density loss. In men, these drugs create a testosterone deficiency state (male estrogen levels are normally very low).

Please let me know if I can be of further assistance.



Lisa Rarick, MD
Medical Officer

Best regards,