

New Approach May Boost Success of IVF

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF
THE AMERICAN SOCIETY FOR
REPRODUCTIVE MEDICINE

DENVER – A bolus of follicle stimulating hormone given at the time of the human chorionic gonadotropin trigger during in vitro fertilization improves the developmental competence of oocytes, a new randomized trial shows.

The result is improved oocyte recovery, a higher fertilization rate, and perhaps a higher pregnancy rate, Dr. Julie D. Lamb said at the meeting.

“These findings may change our current practice, and with further study may play a pivotal role in improving ART outcomes for our patients,” according to Dr. Lamb of the University of California, San Francisco.

She presented a double-blind clinical trial in which 188 IVF patients undergoing a long agonist suppression protocol were randomized to a 450-IU bolus of FSH or placebo at the time of hCG trigger, 36 hours before oocyte retrieval.

VITALS

Major Finding: The measure of fertility rate, consisting of the number of normal fertilized oocytes divided by the total number of oocytes collected, was 63% in the group given an FSH bolus as compared to 55% with placebo, a significant difference. The fertility rate in IVF cycles was 62% with FSH bolus and 48% in controls. In cycles involving intracytoplasmic sperm injection, the rates were 79% with FSH and 73% in controls.

Data Source: A double-blind clinical trial in which 188 IVF patients undergoing a long agonist suppression protocol were randomized to a 450-IU bolus of FSH or placebo at the time of hCG trigger, 36 hours before oocyte retrieval.

Disclosures: Dr. Lamb disclosed having received a research grant from Ferring Pharmaceuticals.

The study rationale was that spontaneous ovulation in most mammalian species is preceded by a surge in FSH and luteinizing hormone, a combined gonadotropin surge believed necessary to final oocyte maturation and follicular rupture.

However, in modern stimulation protocols the last dose of FSH is often given 2 days prior to egg retrieval, and with intentional pituitary suppression little endogenous FSH is present at the pivotal time.

The study hypothesis was that creating a more physiologic ovulation trigger process would improve the developmental competence of oocytes.

“The dramatically increased success in IVF in the last two decades has been attributed largely to improvement in the embryo culture, laboratory conditions,

and optimization of different stimulation protocols. Less attention has been given to different methods of hCG induction of final oocyte maturation,” she said.

The study results indicate this is a fruitful new area. The primary outcome – a measure of fertility rate consisting of the number of normal fertilized oocytes divided by the total number of oocytes collected – was 63% in the FSH group compared with 55% with placebo, a sig-

nificant difference. The FSH bolus improved the fertility rate in IVF cycles, where it was 62% compared with 48% in controls, but not in cycles involving intracytoplasmic sperm injection, where the rates were 79% with FSH and similar at 73% in controls.

Turning to secondary end points, Dr. Lamb reported that the oocyte recovery rate – the chance of obtaining an oocyte upon flushing or aspirating a mature fol-

licle – was 70% in the FSH group, significantly better than the 57% with placebo.

The implantation rate was 40% in the FSH group compared with 35% in the placebo arm. Clinical pregnancy as defined by fetal heart motion on ultrasound occurred in 57% of women in the FSH group compared with 46% of controls. The composite rate of ongoing pregnancy beyond 24 weeks or live birth was 51% in the FSH group and 43% in

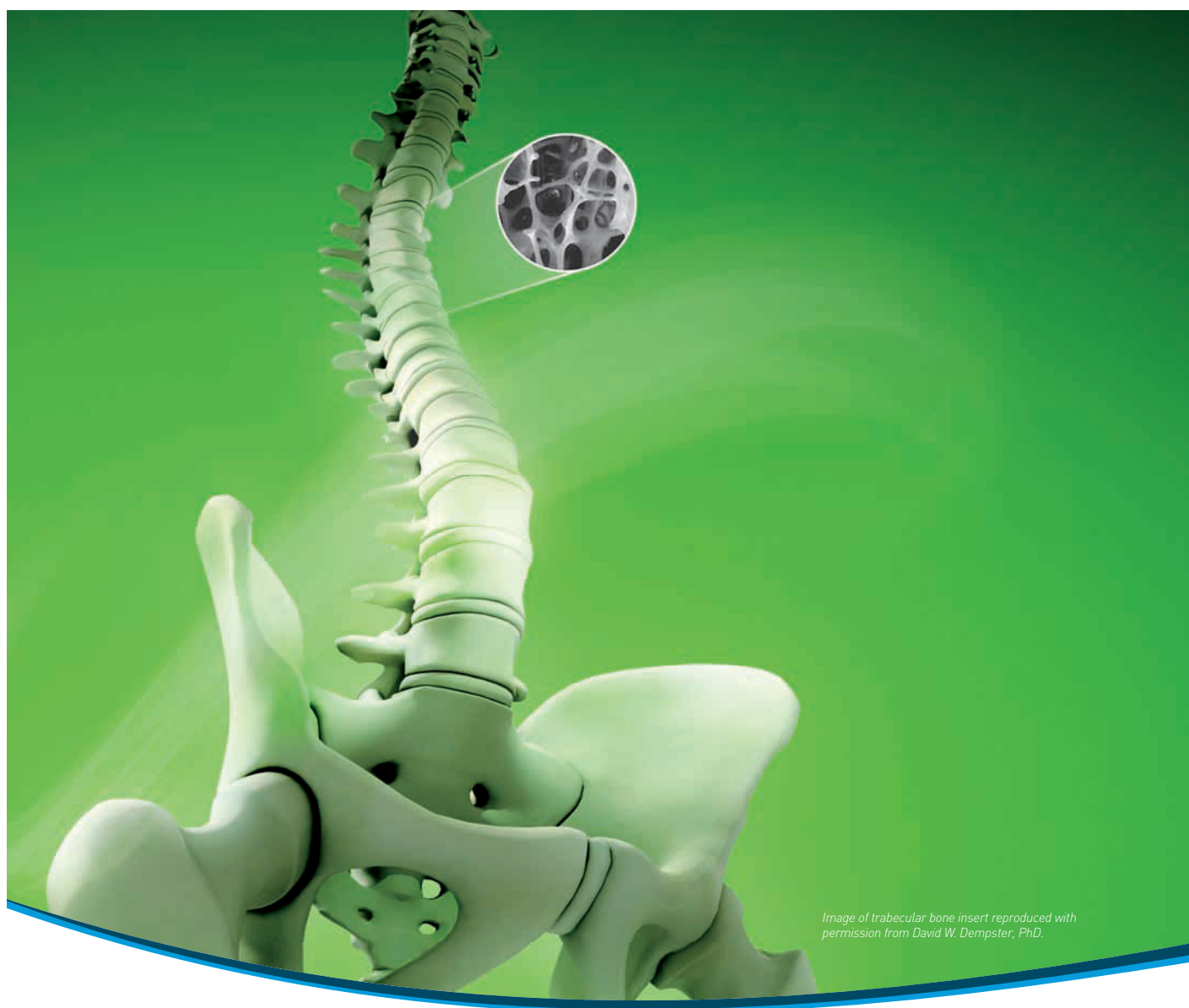


Image of trabecular bone insert reproduced with permission from David W. Dempster, PhD.

INDICATION

Prolia™ is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia™ reduces the incidence of vertebral, nonvertebral, and hip fractures.

IMPORTANT SAFETY INFORMATION

Hypocalcemia: Prolia™ is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia™. Hypocalcemia may worsen, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended. Adequately supplement all patients with calcium and vitamin D.

Serious Infections: In a clinical trial (N = 7808), serious infections leading to hospitalization were reported more frequently in the Prolia™ group than in the placebo group. Serious skin infections, as well as infections of

the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia™. Endocarditis was also reported more frequently in Prolia™-treated subjects. The incidence of opportunistic infections was balanced and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia™, prescribers should assess the need for continued Prolia™ therapy.

Dermatologic Adverse Reactions: Epidermal and dermal adverse events such as dermatitis, eczema and rashes occurred at a significantly higher rate in the Prolia™ group compared to the placebo group. Most of these events were not specific to the injection site. Consider discontinuing Prolia™ if severe symptoms develop.

Osteonecrosis of the Jaw (ONJ): ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia™. An oral exam should

controls. None of these differences were statistically significant. However, the trends consistently favored the FSH intervention. Since the study wasn't powered to show significant differences in pregnancy outcomes, a larger trial will be required to determine whether the FSH bolus truly does boost pregnancy rates, Dr. Lamb said.

Follicular fluid FSH levels on the day of oocyte retrieval were significantly higher in the bolus FSH recipients at 13.3 mIU/mL compared with 9.2 mIU/mL, confirming that the supplemental FSH reached the follicular fluid. The benefits

of bolus FSH weren't due to a change in the broader intrafollicular hormone



A larger trial will be required to determine whether the FSH bolus truly does boost pregnancy rates.

DR. LAMB

milieu, since follicular fluid levels of testosterone, estradiol, progesterone, and

hCG were similar in the two study arms.

No cases of ovarian hyperstimulation syndrome occurred with the study protocol because women with a baseline estradiol level greater than 4,500 pg/mL were excluded from participation as a precautionary measure.

Dr. Lamb said the next step planned by the researchers is a dose-finding study to learn whether a smaller dose of FSH would be equally effective, or if perhaps a larger dose would bring a better response.

She disclosed having received a research grant from Ferring Pharmaceuticals. ■

Ob.Gyn. News

THE LEADER
IN NEWS
AND
MEETING
COVERAGE

Thanks For
Making Us

#1

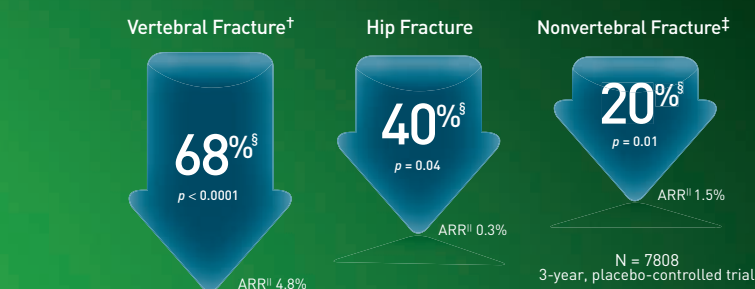
Source: Kantar Media, Media-Chek® Medical/
Surgical June 2010 Readership Summary;
Obstetrics and Gynecology Section, Table 229
High Readers

In Treating Your Postmenopausal Osteoporosis Patients
at High Risk for Fracture, Help . . .

BE A FORCE AGAINST FRACTURE

Prolia™ targets and binds to RANK Ligand, inhibiting osteoclast formation, function, and survival¹

Prolia™ significantly reduced fracture risk at key sites* in a phase 3 trial^{1,2}



Prolia™ is a subcutaneous injection administered every 6 months in your office¹



Please see Brief Summary of Prescribing
Information on the following page.

be performed by the prescriber prior to initiation of Prolia™. A dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with Prolia™.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia™ should be considered based on individual benefit-risk assessment.

Suppression of Bone Turnover: Prolia™ resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for consequences, including ONJ, atypical fractures, and delayed fracture healing.

Adverse Reactions: The most common adverse reactions (> 5% and more common than placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has been reported with Prolia™.

The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia™ groups. A causal relationship to drug exposure has not been established. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

Prolia™ Postmarketing Active Safety Surveillance Program:

The Prolia™ Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please go to www.proliasafety.com or call 1-800-772-6436 for more information about this program.

* Key sites: vertebral, hip, and nonvertebral.^{1,2}

[†] Includes 7393 patients with a baseline and at least one post-baseline radiograph.^{1,2}

[‡] Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.^{1,2}

[§] RRR = relative risk reduction.

^{||} ARR = absolute risk reduction.

References: 1. Prolia™ (denosumab) prescribing information, Amgen. 2. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.

For more information, visit www.ProliaHCP.com

 **prolia**
(denosumab) injection

©2010 Amgen Inc. All rights reserved.
MC48223-C 10-10