

# The Effect of an Oral Contraceptive on Bone Mass in Young, Healthy Premenopausal Women: a two-year prospective study

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## A. Study purpose and rationale

Osteoporosis is a serious health concern characterized by low bone mass and microarchitectural deterioration resulting in bone fragility and increased fracture risk. It affects 25 million Americans and accounts, for 500,000 vertebral, 300,000 hip, and 250,000 Colles fractures a year.

Bone mass increases up to a peak in the third decade of life. Subsequently, there is a short period of slow bone loss followed by rapid bone loss in the peri- and postmenopausal years at rates up to 5% per year. Amongst other risk factors, peak bone mass is a major determinant of subsequent risk for osteoporosis.

Estrogen replacement therapy is important for the treatment and prevention of osteoporosis. It has been shown to increase BMD in postmenopausal women. The role of oral contraceptives on bone mass, however, remains controversial. Retrospective studies have shown that women who used oral contraceptives in the past had higher BMDs than non-users. Investigators looking at the effect of oral contraceptives in perimenopausal women found that there was no bone loss in women taking OC's versus those who had rapid bone loss in the control group. However, there is conflicting evidence of oral contraceptives' effect on bone mass in healthy, premenopausal women.

The purpose of this study is to see if young, healthy premenopausal women using an oral contraceptive formulation [ethinylestradiol 35mcg/norgestimate .25mg] will achieve greater bone growth than those not using a hormonal means of contraception.

## B. Study design and statistical analysis

The study is a prospective, randomized, cohort, controlled parallel arm trial. Following eligibility, subjects would be randomized to either use of oral contraceptive pills [ethinyl estradiol 35mcg/norgestimate .25mg x 21 days/7 days placebo] or nonhormonal method of contraception [i.e. barrier method] and receive counseling on STD and pregnancy prevention. Women would have BMD of lumbar spine [L1-L4] and femur neck measured at baseline, 1 year and 2 years using DXA with a commercial instrument [Hologic QDR 4500A]. The instrument will be calibrated daily using a standardized model provided by the manufacturer. Specialists blinded to treatment arm will read BMD.

Subjects will also be followed at 3mos and every 6mos from baseline measurements for BP measurements, pill counts and compliance to birth control methods, menstrual regularity history, and height & weight measurements. Changes in risk factors would be assessed at baseline and each visit including dietary habits/calcium intake, smoking, and fracture in a first degree relative. Women would receive breast and pelvic exams at baseline and yearly thereafter. They would be monitored for any side effects of each treatment arm. Pregnancy and STI counseling would be offered at each visit.

Data will be evaluated by using an unpaired West to determine the statistical significance of change in BMD gain between groups. Using the unpaired t-test to obtain 80% power to detect an effect of 5% with a standard deviation of 13%, and to account for a possible attrition rate of 20% 161 subjects in each arm will be needed for the study. The standard deviation reflects that provided by the manufacturer based on normative populations of the same age group. A 5% effect conservatively reflects a 2% increase in bone mass in the treatment group above an expected 3.5% increase seen in previous studies of similar women. Data will be subjected to an intention-to-treat analysis. Differences in potential confounders between groups would undergo analysis of covariance.

**C. Study procedures**

Procedures done solely for research purposes are BMD measurements by DXA of spine and femur and initial serum tests to determine subjects' eligibility. Urine ICON will be sent prior to measurements of BMD to r/o pregnancy and avoid any untoward effects of radiation to a fetus. If a woman becomes pregnant, BMD measurements will be avoided until a period deemed safe to the pregnancy and she would be referred for the proper counseling and care.

Blood pressure monitoring and questionnaires regarding OC side effects will be taken at each visit to monitor for side effects. Subjects will receive breast and full gynecologic exams yearly as part of standard health maintenance.

**D. Study drugs**

An FDA approved formulation of oral contraception using EE 35mcg/norgestimate .25mg for 21 days with 7 day placebo. Norgestimate is a third generation progestin noted to have fewer side effects than earlier formulations. This formulation is effective for contraception and mainly safe in the population to be studied. Common side effects include nausea, bloating, altered menses, breast tenderness, and edema. Serious reactions such as thromboembolism, MI, HTN, CVA, and hepatic adenoma are extremely rare in this group for this duration of use.

**E. Medical devices**

None

**F. Study questionnaires**

Questionnaires will be designed for dietary habits and aforementioned variables at baseline and follow up visits.

**G. Study subjects**

Participants will be women, ages 19-29, in general good health as confirmed from a note by their physician who are willing to use oral contraceptives as a method of birth control and have no previous history of OC use or other means of hormonal contraceptive therapy.

Exclusion criteria are smokers, women with conditions or on medications affecting bone mass, women who are pregnant or lactating or have experienced premature menopause, and women who have a history of heart disease, stroke, blood clots/PE, liver cancer, breast cancer, gallbladder disease, or hypertension.

Screening tests to determine eligibility at baseline will include BP, serum Ca, TSH, LFTs, urine ICON, FSH/LH, BUN/Cr, breast exam, pelvic exam and Pap smear [if not already done in previous 3 mos and documented by PMD].

**H. Recruitment of Subjects**

Subjects will be identified by responses to advertisements in local newspapers, flyers or referrals from clinicians at Medical, Gynecologic, and Family Planning clinics at CPMC and affiliated clinics.

**I. Confidentiality of study data**

Study data will be coded with a number I to 262 and randomly assigned to subjects. Data will be stored in a secure location, accessible only to the investigators.

**J. Potential Conflict of Interest**

None

**K. Location of the study**

The study will proceed at CPMC outpatient clinics.

**L. Potential Risks**

Risk of pregnancy and STDs is a concern for these subjects. Participants will be provided with an emergency contact number if symptomatology arises. Risks secondary to OC use are small and have been previously described.

**M. Potential Benefits**

For those randomized to OC use, benefits may include improved acne, reduced risk of endometrial and ovarian cancers, reduced dysmenorrhea and menorrhagia. The study would allow women to obtain free medical and gynecologic care and contraception during the study period.

**N. Compensation to Subjects**

Subjects would be offered a predetermined monetary compensation at each visit and bonus at completion of the study. Also, they would be offered a year of free OC's at completion of study.

**O. Costs to subjects**

None

**P. Radiation**

Radiation exposure is minimal, 0.20mGy for spine and 0.20mGy for hip. Urine ICON will be sent prior to each BMD measurement.

## Information Sheet

### Columbia Presbyterian Medical Center Participation in a Research Study

*The purpose of this form is to provide you with the information you need to understand the research study in which you are participating.*

**Study title:** A Randomized Controlled Trial Comparing the Rates of Bacterial Colonization of Nontunneled Internal Jugular Vein Catheters and Femoral Vein Catheters.

#### Study Purpose

You are participating in a research study looking at contamination of intravenous catheters (also known as an "IV") by bacteria and fungus. Studies have shown that catheters that are inserted in the veins (blood vessels) in the neck and thigh have a higher rate of bacterial contamination than those placed in the arm. No study has appropriately compared the rate of contamination of catheters in the neck with the rate of contamination of catheters in the thigh. This study will compare the rates of catheter contamination in those two sites.

You qualify as a participant in this study because you are (or will shortly be) hospitalized in an Intensive Care Unit at Columbia Presbyterian Medical Center (New York Presbyterian Hospital) and your doctor has decided that you require a catheter to be placed in a vein in your neck or your thigh. A total of 660 patients at Columbia Presbyterian Medical Center will be enrolled in this trial.

#### Study Procedures

An intravenous catheter will be placed in a vein in your neck or in a vein in your thigh. You will be assigned by chance to receive the catheter in your thigh or in your neck. This procedure will be performed by one of the doctors in the intensive care unit, operating room, emergency room, or on the hospital floor. Catheter placement begins with thorough cleansing of the neck or thigh with an iodine-containing solution. Then a sterile sheet is placed over your body, and the doctor will insert a needle into one of the veins in the neck or thigh. A wire will be inserted through the needle into the vein, and a plastic catheter will be threaded over the wire into the vein. The wire is then removed from the vein and the catheter is stitched into place and covered with a clear dressing.

The catheter used and the technique described above are not experimental. Your doctor has already determined that you require a catheter to be placed as described above. Your entry in this study determines only where the catheter will be placed.

Your doctors in the intensive care unit as well as physician members of the research team will monitor you for complications related to the catheter. The doctors in the intensive care unit will determine when you require blood tests and x-rays for your medical care. Your enrollment in this study will not result in the performance of any extra or unnecessary tests.

You will be enrolled in this study until the catheter is removed. Usually these catheters remain in place for 1-7 days. Occasionally the catheter will stay in for up to one month or more. The catheter will be removed when medically necessary or when not needed anymore (as decided by you ICU doctor). If you receive another catheter later in your hospital stay, you may or may not be reenrolled in this study.

#### Study Risks

The risks associated with intravenous catheters are as follows:

- (1) Those patients who receive a catheter in the neck are at risk for developing a collapsed lung (pneumothorax). This complication is rare, is routinely screened for after every procedure, and is treatable with a minor bedside procedure. Most patients will not develop a collapsed lung.

- (2) Those patients who receive a catheter in the neck are at risk for a rare complication known as "air embolus." This complication occurs when air is pulled into the vein and travels to the lung, blocking blood flow through the lung. Routine precautions are taken to prevent this complication.
- (3) Other risks, regardless of the location of the catheter, include infection, bleeding, clots in the veins, placement of the catheter outside of the vein (for example, in an artery or muscle), and local pain and discomfort.

These risks are the same for all catheter placements in the hospital whether or not you are enrolled in this study. You will not be at a higher risk of complications by enrolling in this study.

### **Study Benefits**

You will not benefit personally from this study.

Benefits to society include a better understanding of how catheter location influences the rate of bacterial contamination. The results of this study may help doctors decide which location is preferable.

### **Costs**

No additional cost will be incurred by you for enrollment in this study.

Costs that are incurred by medically necessary care will be billed to you or your insurance company. After your catheter is removed, it will be sent to the laboratory to look for bacteria. You will only be responsible for the charges related to this test if your doctor would have ordered it outside of the study.

### **Compensation**

You will not receive monetary compensation for your participation in this study.

### **Confidentiality**

Any information obtained during this study and identified with you will remain confidential. All research material which personally identifies you will be kept in a locked office in Milstein Hospital. Only Drs. Chong and Lederer will have access to that information.

### **Questions**

If you have any questions, please ask, and we will do our best to answer them. IF you have additional questions in the future, you can reach Dr. Chong at (212) 305-6751.

If you have any questions on your rights as a research subject, you can call the Institutional Review Board at (212) 305-5883 for information.