USE OF NORETHINDRONE ACETATE FOR MANAGEMENT OF BLEEDING ASSOCIATED WITH THE ETONOGESTREL CONTRACEPTIVE IMPLANT

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HYPOTHESIS:

Oral progesterone is a useful therapy for the management of bleeding associated with the etonogestrel contraceptive implant.

OBJECTIVE:

The overall objective of this study is to confirm that oral progesterone is an effective way to manage bothersome bleeding; thus increasing the rate of continuation of the etonogestrel contraceptive implant in adolescents.

BACKGROUND AND SIGNIFICANCE:

Of the approximately three million pregnancies annually in the United States, 50 percent are unintended pregnancies. Adolescents bear a significant burden of such unintended pregnancies, with 82 percent of adolescent pregnancies being unplanned (1). It is well documented that adolescent pregnancies have deleterious effects on women's health and educational attainment, the health of newborns, and incur a significant emotional and financial burden, both for the individual and society as a whole. Furthermore, greater than one-third of unintended adolescent pregnancies end in abortion (2).

While most sexually active adolescents report using a method of contraception at some point in their lifetime - they are not typically selecting the most effective methods. Combined oral contraceptives and condoms are the most popular and most requested method of contraception by teenagers (3, 4). Unfortunately, the failure rates of both oral contraceptives and condoms among adolescents are higher compared with all typical users (5, 6). Specifically, adolescent mothers are

documented to have a high rate of repeat pregnancy and are more likely to use ineffective methods and to use effective methods inconsistently or incorrectly (6).

It is encouraging that there has been in increase in the number of adolescents who use long-acting reversible contraceptive (LARC) methods, such as the intrauterine device or contraceptive implant. With 4.5% of adolescents using such methods in 2009, compared to only 1.5% in 2007, and just 0.3% in 2002 (7). In fact, when adolescents were counseled on the full range of contraceptive options and the barrier of cost for LARC methods was removed in a large study, more than two-thirds of females aged 14 – 20 years chose LARC methods (8). It is also promising that national organizations, such as the American Congress of Obstetricians and Gynecologists, have emphasized the importance of LARC method use by adolescents. Specifically, ACOG states that LARC methods are safe and appropriate for most women and adolescents, and that they provide top-tier effectiveness, high rates of satisfaction and continuation (9). Furthermore, the Contraceptive CHOICE project, a large prospective cohort study designed to promote the use of LARC methods to reduce unintended pregnancy, found that sexually active teens using the contraceptive implant or intrauterine device have significantly lower mean annual rates of pregnancy, birth, and abortion (34.0, 19.4, and 9.7 per 1000 teens) compared to sexually experienced U.S. teens (158.5, 94.0, 41.5 per 1000) (10). Data from the contraceptive CHOICE project also demonstrates that teens continued to use LARC methods longer than shorter acting methods (i.e. the oral contraceptive pill and depot medroxyprogesterone acetate injections) – two thirds of teens in the CHOICE project were still using their LARC method at 24 months, as compared with only one third of teens using a non-LARC method (11).

The sub-dermal single rod etonogestrel-only implant offers highly effective, long-acting, reversible contraception (12). It consists of a single rod (4 cm in length, 2 mm in diameter) made of ethylene vinyl acetate, containing 68 mg of etonogestrel that is released subdermally over three years. Prevention of pregnancy is accomplished by several mechanisms – suppression of ovulation, thickening of

cervical mucus inhibiting sperm penetration into the uterus, and alteration of the endometrium. In the clinical trial of 301 Nexplanon (the radiopaque etonogestrel implant) users, no woman became pregnant while the implant was in situ, up to and including 14 days after implant removal. This resulted in an estimated overall Pearl Index of 0.0 (95% CI, 0.0 – 0.56) (12); which translates clinically to >99 percent effective at preventing pregnancy. They are documented to be safe for use in the adolescent population. However, the implant is currently used by less than 1% of U.S. women using contraception, and by 0.5% of those aged 15-19 years (13).

It is well documented that women using the contraceptive implant can expect changes in their menstrual bleeding patterns, and these changes account for the most commonly cited reason for method discontinuation. The bleeding pattern women experience in the first three months after insertion is predictive of future bleeding patterns throughout the duration of use (14). When analyzing 11 clinical trials, bleeding patterns were described as infrequent bleeding in 33.3% of 90-day cycles, amenorrhea in 21.4% of cycles, prolonged bleeding in 16.9% of cycles, and frequent bleeding in 6.1% of cycles (15).

There have been studies that propose management options for treating bothersome bleeding associated with the etonogestrel contraceptive implant – such options include combined oral contraceptive pills, non-steroidal anti-inflammatory agents, mefenamic acid, mifepristone, and doxycycline. Unfortunately there is limited clinical data supporting the effectiveness of these treatments (16-18). To our knowledge, there have been no studies investigating the use of oral progesterone for management of bothersome bleeding associated with the contraceptive implant. Given the success of norethindrone acetate in the management of pain and bleeding in adolescents with endometriosis (19), we chose to use norethindrone acetate as our oral progestin of choice for managing bothersome bleeding associated with the contraceptive implant.

When investigating bleeding patterns, a common challenge encountered is that of patient compliance with menstrual calendars. The burden of keeping a daily menstrual calendar may lead to reduced response rates, incomplete data, and poor data fidelity. The widespread popularity of mobile phone technology has increased the ability to connect with study participants in real time, thus decreasing the reliance on traditional pencil and paper methodology for data collection. There are several potential advantages for using short-message service text messaging (SMS) for data collection: (a) data is time stamped thus providing accurate real-time information, (b) study designers have the ability to ensure data responses conform to a set criteria, (c) automatic SMS texts provide prompts for participants to record the data of interest, (d) data transfer is instantaneous thus reducing data loss or incompleteness, and (e) data collection is more convenient and accessible for participants as they are likely to have their mobile phone devices with them and be familiar with the SMS texting function of their particular device. To our knowledge there have been no studies that use SMS text messaging to record data on daily bleeding patterns – essentially creating a real-time electronic menstrual calendar.

MATERIALS AND METHODS:

We will conduct a prospective study of adolescents using the etonogestrel contraceptive implant. Participants will be recruited from the Norton Children's Gynecology practice in Louisville, Kentucky. This practice provides care to a diverse population of females, from a wide range of socioeconomic statuses, age birth to 25 years.

Inclusion criteria will include any post-menarchal female presenting to the Norton Children's Gynecology practice, who desires to use the etonogestrel contraceptive implant and has access to a mobile phone device.

All patients presenting and choosing to have an implant placed will be offered participation. The study will enroll subjects until 30 active participants are in each study arm; for a total of 60 study participants. In order to achieve the enrollment of

60 active subjects up to 100 participants will be enrolled. All enrollments will be voluntary. Participants will receive compensation for their participation. After obtaining informed consent and assent, participants will provide baseline demographic information, including: age, race/ethnicity, zip code of residence, health insurance provider, number of current and past partners, use of prior contraceptive methods, concomitant condom use, sexually transmitted infection history, age at menarche, menstrual cycle regularity, last menstrual period, weight and height. The date of etonogestrel implant insertion will be confirmed.

All patients using etonogestrel contraceptive implants will receive daily SMS texts in the evening via the Qualtrics SMS program asking them to respond with their bleeding pattern that day. If the SMS text messages are unable to connect to your personal cell phone we request an alternative cell phone number be given in order to reach you. We will record responses according to the World Health Organization definitions of bleeding: (a) bleeding day, (b) spotting day, (c) bleeding-free day [see Table I for WHO bleeding definitions]. At their initial follow-up visit 3 months after Nexplanon insertion, we will identify those who report "bothersome" bleeding patterns. For the purpose of this study, "bothersome" bleeding will be defined as prolonged and/or frequent bleeding, as characterized by World Health Organization-recommended definitions of bleeding. The definitions are listed in Table I.

Bleeding day	Any day with vaginal discharge containing blood that required more than 1 sanitary pad or tampon per day
Spotting day	Any day with vaginal discharge containing blood that required at most one sanitary pad or tampon per day
Bleeding-free day	A day during which neither bleeding nor spotting was reported
Bleeding-spotting episode	One or more consecutive days during which bleeding or spotting was entered in the diary, bounded by bleeding-free days
Amenorrhea	No bleeding or spotting days throughout the 90-day reference period
Infrequent bleeding	Less than three bleeding-spotting episodes in a 90-day reference period, excluding amenorrhea
Normal frequency	Three to five bleeding-spotting episodes in a 90-day reference period
Frequent bleeding	More than five bleeding-spotting episodes in a 90-day reference period
Prolonged bleeding	Any bleeding-spotting episode (uninterrupted) lasting more than 14 days in the 90-day reference period

Table I: WHO bleeding descriptions and patterns

Norethindrone acetate (aygestin) will be used to manage bothersome bleeding. Patients will be prescribed aygestin 5 mg by mouth twice daily for one month, followed by aygestin 5 mg by mouth once daily for two months. Medication will then be discontinued. Patients will be evaluated in the office three months after medication initiation, and then again six months after medication initiation. If the patient is unable to take norethindrone acetate (aygestin) due to medical contraindications or cost, they will receive medroxyprogesterone acetate (provera) 10 mg once daily as alternate oral progesterone. Figure 1 below highlights the study design.

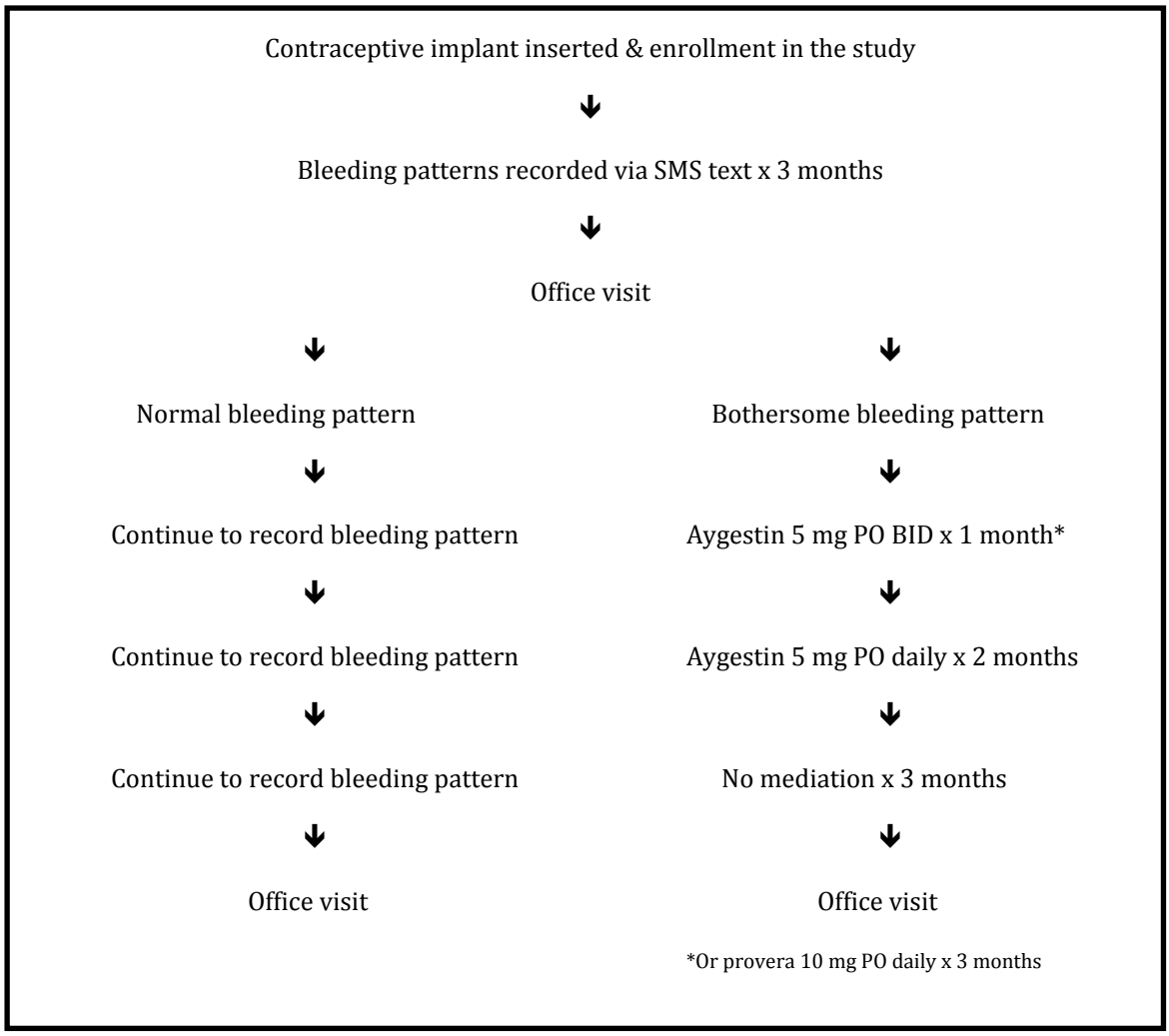

Figure 1: Study design

During the aygestin administration, patients will again receive daily SMS texts in the evening via the Qualtrics SMS program asking them to respond with their bleeding pattern that day. We will record responses according to the World Health Organization definitions of bleeding: (a) bleeding day, (b) spotting day, (c) bleeding-free day. Patients not reporting bothersome bleeding after the initial 90 days will continue to record bleeding via SMS texts for the next 6 months to serve as the control group (normal bleeding group).

Participants will be compensated as an incentive to increase daily participation. The participant will receive a pre-paid card if they respond to >70% of text messages over each 90-day cycle and attend the scheduled office visit. Patients will receive a $5 pre-paid card at visit one (3 months after insertion of etonorgestrel implant), $10 pre-paid card at visit two (6 months after insertion of etonorgestrel implant), and a $15 pre-paid card at visit three (9 months after insertion of etonogestrel implant).

At the completion of the study, 9 months after enrollment, participants will receive a SMS text message via Qualtrics with a link to a 12 question follow up survey. The post study questionnaire will assess overall satisfaction with the etonogestrel implant and evaluate participants' perceptions of text messaging as a tool to collect information. See Appendix II.

Participants who have already completed the 9 month study will receive an updated copy of the consent and assent form via mail with a request to sign the updated consent and assent forms. See Appendix III for a copy of a letter to be included with the updated consent and assent. Once the updated consent and assent are received by the investigators at Norton Children's Gynecology the post survey follow up will be sent to the participant by SMS text message via Qualtrics. Study participants who are seen in the office for their 9 month follow up visit will be re-consented in the office.

Patients diagnosed with a sexually transmitted infection during the course of the study will be removed from the study and their data will be excluded from analysis.

All completed demographic data collection forms and electronic menstrual calendars will be kept in a database, de-identified, and stored on a password-protected computer. Study size will be a convenience sample. Based on the current rate of etonogestrel implant insertions in our practice, it is anticipated that 30 participants can be recruited over a six-month period of time.

Data Collection and Analysis

All patients who meet the inclusion criteria and enroll in the study will be sent a text message daily for 90 days (3 months). The daily message will prompt the participant to indicate the bleeding level for the day. This single question will have 4 options:

1. Bleeding Day
2. Spotting Day
3. Bleeding Free Day
4. Prefer not to answer today.

On day 90, descriptive tallies of the responses will be done. Using SPSS v20, an algorithm will count the number of bleeding days, spotting days, and bleeding free days and prefer not to answer (PNA) days; the data record for each participant will contain four count variables (bleeding, spotting, free, PNA). Secondly, the algorithm will identify and tally –according to WHO guidelines in Table 1 - bleeding-spotting episodes (BSE), amenorrhea (AM), infrequent bleeding (IF), normal frequency of bleeding (NF), frequent bleeding (FB), and prolonged bleeding (PB).

Participants who have at least a single episode of FB or PB will be assigned the label of "bothersome bleeding". Those without a single episode of FB or PB will be labeled "normal bleeding". Participants in the Bothersome Bleeding group will be offered aygestin to control the bothersome bleeding. Participants in the Normal Bleeding group will continue as before, with no additional medications. Following the principle of intent-to-treat, data from those in the Bothersome Bleeding group will be assigned to the aygestin group, despite that they are not taking it.
During the first month, participants in the Bothersome Bleeding group will take one 5 mg tablets of aygestin twice daily (morning and evening). After 30 days, the dose of aygestin will be halved, such that only one 5 mg tablet is taken daily. Sixty days

later, the Bothersome Bleeding group will discontinue aygestin. Ninety days later, both the normal group and the Bothersome Bleeding group will be re-evaluated.

Data Analysis

A descriptive table will be used to sort participants into Normal Bleeding and Bothersome Bleeding. Non-parametric and parametric statistics will be used to compare the demographics of these two groups.

A **dose-response curve** covering six months will be plotted for the Bothersome Bleeding group to visually reveal the impact of one month of 10 mg of aygestin vs. two months of 5 mg aygestin vs. three months 0 mg of aygestin. Plotted on the curve will be the group averages of the daily bleeding value (1 for no bleeding, .5 for spotting, 0 for bleeding). A second **no-dose curve** will be added to the X-Y plot for the six months of data from the Normal Bleeding group.

Repeated Measure Multivariate Analysis of Variance (RM-ANOVA) with a Between-Subjects variable included, will be conducted (assuming sufficient data is available – e.g., low PNA rates) to compare the first 30 day average bleeding value, the 90 day bleeding average, and the 180 day bleeding average between the two groups. Planned post-hoc comparisons will evaluate changes between the control group and intervention group at the three time points.
Additional analyses may also include regression analysis to assess for predictive factors related to response to aygestin.

TIMELINE:

October 2014	IRB Submission
November 2014	Anticipated IRB Approval
November 2014 – July 2015	Data Collection
August – September 2015	Data Analysis
October 2015	Submission of preliminary data to the North American Society for Pediatric and Adolescent Gynecology (NASPAG) Annual Clinical and Research Meeting Board
April 2016	Present at the North American Society for Pediatric and Adolescent Gynecology (NASPAG) Annual Clinical and Research Meeting
May 2016	Final manuscript composition and submission for publication

APPENDICES:

Appendix I: Demographic Data Collection Form

INFORMED CONSENT / ASSENT:

See the attached University of Louisville Biomedical Informed Consent and Assent Forms.

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APPENDIX I:

DEMOGRAPHIC DATA COLLECTION FORM:

What is your age?
_____ Years old

Are you Hispanic or Latino?
_____ Yes, Hispanic or Latino
_____ No, not Hispanic or Latino

How would you describe yourself? Choose one or more from the following ethnic/racial groups:
_____ American Indian or Alaskan Native
_____ Asian
_____ Black or African American
_____ Native Hawaiian or Pacific Islander
_____ White

What is your zip code?
_____

Health insurance provider
_____ Private insurance
_____ Medicaid (i.e. passport)
_____ No insurance

Sexual partners
_____ In the past month
_____ In your lifetime

Use of prior contraceptive methods
_____ Pills
_____ Patch
_____ Ring
_____ Depo-Provera
_____ Intrauterine device
_____ Condoms
_____ Spermicide
_____ Sponge
_____ Diaphragm
_____ Withdrawal

Are you currently using condoms?
_____ Most / All of the time
_____ Some of the time
_____ None of the time

Have you ever had a sexually transmitted infection?
_____ Chlamydia
_____ Gonorrhea
_____ Trichomonas
_____ Herpes
_____ HIV / AIDS
_____ Hepatitis B
_____ Hepatitis C
_____ Syphilis

How old were you when you started having periods?
_____ Years old

Are you currently having a monthly menstrual cycle?
_____ Yes
_____ No

What was the first day of your last menstrual period?
_____

What is your weight?
_____ Pounds

What is your height?
_____ Inches

When was your implant put in?
_____ Date

Appendix II:

1	How do you feel about using text messages as a way of telling the researchers about your period or break-through bleeding?	Very happy	Happy	Neutral	Un-happy	Very Un-happy
2	Did you answer the text messages every day?	All of the time	Most of the time	Some of the time	Hardly ever	Never [1]
3	When you were not able to answer the text message, what were the reasons for not doing so? Choose all that apply	Busy doing some-thing else	Forgot about to answer	Lost access to my phone	Ran out of minutes/ texts	Other
4	Did you ever feel annoyed or unhappy about receiving texts from the researchers?	No, never	Rarely	Some-times	About once a week	Every day
5	Would you be more or less likely to enroll in a future study if that study also used text messages to collect your information?	Much less likely to enroll	Less likely to enroll	Makes No differ-ence	More likely to enroll	Much more likely to enroll
6	Text messages were sent at 6pm every evening. How did you feel about the timing of the texts?		Better earlier in the day	The timing was fine	Better later in the day	
7	For this type of research, another way of collecting data is to have you write your information into a paper-based diary each day. Which method of data collection would you prefer?	Strongly prefer paper-based diary	Prefer paper based diary	Either would be fine	Prefer text-based	Strongly prefer text-based
8	Throughout the study period (up to 270 days), how often did you change your cell phone plan (for example, get a new phone number, change your plan to get more or fewer messages, etc.)?	Never	1 time	2 times	3 times	More than 3 times
9	Did the text message format make it easier or harder for you to give your answer truthfully?	Much Easier	Easier	No differ-ence	Harder	Much Harder
10	How likely do you think your friends would be willing to enroll in a study that uses text messaging for collecting data?	Very likely	Likely	Neither likely nor unlikely	Unlikely	Very unlikely
11	Do you plan to keep your Nexplanon for the next 9 months or longer?	Already removed it	No	Un-decided	Yes	
12	Would you recommend Nexplanon to a friend?	Definitely no	Maybe no	Undecide d	Maybe yes	Definitely yes

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Appendix III:

Norton Children's Gynecology
3991 Dutchmans Lane, Suite 303
Louisville, KY 40207

Dear Study Participant,

You had participated in an etonogestrel contraceptive implant (Nexplanon) study for 9 months. We have created a 12-question follow up survey to evaluate your satisfaction with the Nexplanon and your perception of text messaging as a tool to collect information. We would like to send you a text message with a link to the post study survey.

Enclosed you will find an updated copy of the Consent and Assent forms. You had completed these Consent and Assent forms in the office 9 months ago. These updated documents however now include information about the 12-question follow up survey. The Consent is updated on page 2, paragraph 5 and the Assent is updated in paragraph 4. Prior to sending you a text message link to the post study survey both the Consent and Assent forms will need to be signed and mailed back to our office.

We would appreciate if you could please read the documents and then have the participant's guardian sign the Consent form on page 8 and the study participant sign the Assent form on Page 2. These documents can then be placed in the enclosed return envelope and mailed to our office.

Thank you for your participation in the study as we value your input. Should you have any questions about the survey or enclosed documents please call our office to speak with study personnel at (502) 559-1750.

Thank you,

Rachael Polis, DO