My ten-week internship was based in New York at Bellevue Hospital and I worked closely with my supervisor, Dr. Miriam Cremer, on a chapter review on *New Formulations of Oral Contraception* for the journal, Seminars in Reproductive Medicine. This research project was a huge component of my internship. In writing the chapter review, it not only strengthened and improved my writing skills, but also taught me fundamental aspects of writing such as organization, structure, formatting, and style.

Before conducting a literature search and writing the chapter review, I had no prior knowledge of research. Much of what I learned and took away from this research project was understanding and familiarizing myself with a new language. As I read through a lot of the literature on the new regimens (24/4, 84/7, and Lybrel) and newer progestins (drospirenone and cyproterone acetate) available on the market in the United States, I began to understand a new writing style. Reading through the literature not only educated me on the subject of new formulations available to women, but also cemented in me a new style of writing that I could apply to all of my future research.

Throughout the writing process, I began to think deeply about contraception in a general sense and its role in women’s lives. I also thought very deeply about the importance of women having access to contraception in the United States and globally. Having thought about these things really made me enjoy writing the chapter review. It made me feel that I was making a small contribution towards women gaining access to contraception and also making aware to the general public what formulations are available and most effective and safe for contraception users. With that said, I really wanted to share my research this summer by enclosing a draft
ABSTRACT

Since the 1960s, oral contraceptives were administered in a traditional 21/7 regimen. In recent years, new regimens (24/4, 84/7, and Lybrel) have reported that shortening the HFI decreases the risk of ovulation and unintended pregnancy. Recent literature also suggests that these regimens are associated with breakthrough bleeding and amenorrhea in extended and continuous-cycle regimens.

KEYWORDS: 24/4 regimen, 84/7 regimen, Lybrel, DRSP, CPA

Oral contraceptives (OCs) are widely used among women of reproductive age for the prevention of pregnancy and continue to remain a common method of reversible contraception. Prior to the approval of extended (24/4 and 84/4) and continuous-cycle (Lybrel) regimens, most OC regimens were packaged in the traditional form of a 21/7 regimen, with 21 days of active or hormone-containing pills and 7 days of a placebo or a hormone-free interval (HFI). The standard cyclic regimen included an induced monthly withdrawal bleed resembling a woman’s natural menstrual cycle during the HFI and thereby increased acceptability in women. In recent years, the induced monthly withdrawal bleed during the traditional 7-day HFI has been challenged by several studies. Surveys purported that some women prefer a reduction in the number of menses per year. Another study reported that decreasing the HFI of contraceptive regimens from 7 days to 3 or 4 days inhibits ovarian hormone production more effectively than the traditional 21/7 regimen. In an effort to reduce or eliminate withdrawal bleeding episodes, modifications to these formulations of OCs have primarily involved lowering the hormone content and utilizing newer progestins such as drospirenone (DRSP) and cyproterone acetate (CPA) to decrease the risk of ovulation and unintended pregnancy and hormone withdrawal symptoms associated with menstruation. This chapter will therefore address issues related to new formulations of OCs, particularly where efficacy, risks, and effect on menses associated with these new formulations and newer progestins are concerned.

4. Sulak PJ, Kuehl TJ, Ortiz M, Shull BL. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms. Am J Obstet Gynecol 2002; 186: 1142-9
NEW REGIMENS

COCs were first introduced in the United States in the 1960s. In recent years, the FDA approved new COCs given in the following regimens: 24/4 regimen, 84/7 regimen, or continuous use regimen. These agents contain 20 mcg EE and 3 mg DRSP (24/4), 20 mcg EE and 1 mg norethindrone (24/4), 30 mcg EE and 150 mcg LNG (84/7 regimen) with a very low-dose of EE (10 mcg/day) for 7 days, and 20 mcg EE 20 and 90 mcg LNG taken continuously. These new regimens, classified as either extended or continuous-cycle OCs, differ from traditional cyclic regimens with respect to a decrease in hormone content, thereby altering the length of the menstrual cycle. Shortening the HFI in new contraceptive regimens decreases the frequency of menses to four times per year or eliminates menses altogether and suppresses ovarian hormone-production more effectively than traditional cyclic regimens. OCs have been used in the treatment of dysmenorrhea, endometrial cancer, abnormal uterine bleeding, acne and POS. 1,2

1. Willis SA, Kuehl TJ, Spiekerman AM, Sulak, PJ. Greater inhibition of the pituitary-ovarian axis in oral contraceptive regimens with a shortened hormone-free interval.


24/4 Regimen

Since the 1960s, traditional oral contraceptives were administered in a 21/7 regimen. A shorter HFI was created to minimize contraceptive failures and adverse side effects associated with oral contraceptive use. The 24/4 regimen is one of two types of extended-cycle OCs that delivers 24 days of low-dose combination (progestin-estrogen) followed by 4 days of inert or hormone-free tablets. There are currently two formulations that are FDA-approved for a 24/4 regimen: DRSP/EE 3 mg/20mcg (YAZ) and norethindrone acetate/EE 1 mg/20 mcg (Loestrin 24 Fe). These products are designed for the occurrence of withdrawal bleeding every month. The 24/4 regimen is approved in the United States for preventing pregnancy in women and for the treatment of premenstrual dysphoric disorder (PMDD) and acne.


84/7 Regimen

The 84/7 regimen is the second type of extended-cycle OC that contains 84 days of low-dose combination (progestin-estrogen) pills followed by 7 days of a very low-dose estrogen (10 mcg/day). At present, EE/LNG 30 mcg/150 mcg (Seasonique, Duramed) is FDA-approved for an 84/7 regimen that results in 4 withdrawal bleeding episodes per year instead of 13 with the traditional 28-day-cycle OCs. Seasonique, a derivative of EE/LNG 30 mcg/150 mcg (Seasonale, Duramed), decreases withdrawal symptoms associated with menstruation. 1,2
Safety and Efficacy

OCs are one of the most commonly used methods of contraception in the United States. A careful assessment of the safety and efficacy of OCs remains important in contraceptive users. Recent studies on the safety and effectiveness of *Seasonale* and *Seasonique* conclude that the 91-day extended regimen is safe and effective in preventing ovulation and pregnancy.\(^2\)\(^-\)\(^4\) In 2003, a 1-year multicenter, open-label study of *Seasonale* in sexually active women aged 18 to 40 years was performed to assess its safety profile and efficacy. In this study, the extended cycle regimen was effective in preventing pregnancy and its safety was comparable to that of traditional cyclic regimens. Though breakthrough bleeding was reported in women given the extended regimen, reports also indicated that unscheduled breakthrough bleeding diminished with each successive cycle. Pearl Index based on method failure was 0.60 for *Seasonale*.\(^2\) Similar results on the safety and effectiveness were reported in a 1-year multicenter, open-label study of *Seasonique*. In this study, assessment of efficacy and safety reported that *Seasonique* was tolerated for the prevention of ovulation and pregnancy. Pearl Index based on method failure was 0.78, similar to that of *Seasonale*.\(^3\) In summary, the safety profile and effectiveness of extended regimens like the 84/7 regimen were demonstrated in women and the extended regimen was comparable in safety and efficacy in other COCs.

Bleeding Patterns

A number of studies have demonstrated that OC use is associated with unscheduled breakthrough bleeding or spotting during the HFI but diminish with continued use of OCs. A 1-year cross-study analysis was conducted to examine bleeding patterns in women using two different 91-day extended OC regimens. One group of women was given a 91-day extended regimen containing 10 mcg EE and the other group was given a placebo interval. When comparing the two, unscheduled breakthrough bleeding with the extended regimen containing 10 mcg EE had decreased more quickly that that of the placebo interval group during cycle 3. Thus, the bleeding profile of an extended regimen containing 10 mcg EE improves more quickly that that of extended regimens containing a placebo interval.\(^5\) In summary, women experienced a decrease in unscheduled breakthrough bleeding during the extended 28-day regimen than the standard, 21/7 regimen.

Endometrial Effects

In recent years, there has been some concern that greater exposure to estrogen may be associated with increased risk for endometrial cancer. Recent studies suggests otherwise. In a 1-year multicenter, randomized, open-label study conducted at seven sites in the United States on a cohort of women receiving a 91-day extended regimen containing 84 days active combination tablets (30 mcg EE/150 mcg LNG) followed by a 7 days of 10 mcg EE tablets in place of a placebo interval, endometrial biopsies were performed and results indicated that this extended regimen did not show changes in the endometrium.\(^6\) Similarly, to assess changes in the endometrial microstructure of the extended regimen OC, Anderson et al. conducted a cohort study in women who were treated with a 91-day extended regimen. It was reported that there was no statistical difference in the endometrial lining in a compared to the traditional 21/7.\(^7\) In summary,


LYBREL – A CONTINUOUS ORAL CONTRACEPTIVE

Lybrel (Wyeth Pharmaceuticals) became available in the United States in 2007 as the first FDA-approved combination (progestin-estrogen) oral contraceptive (COC) taken daily and is marketed for continuous-cycle oral contraceptive use in women. The tablets contain low doses of levonorgestrel (LNG) 90 mcg and ethinyl estradiol (EE) 20 mcg. Unlike other OC regimens, Lybrel does not have a HFI and is thereby intended to eliminate menstruation.

Efficacy

Two large 1-year, open-label clinical studies were conducted to demonstrate the contraceptive efficacy of Lybrel. The first study revealed that among 2,134 women, a total of nineteen women became pregnant during the continuous LNG/EE regimen, a Pearl Index (the number of pregnancies per 100 women per year of use) of 1.60. Fifteen of the nineteen women who became pregnant were attributed to method failure, a Pearl Index of 1.26, and the other four were attributed to user failure, a Pearl Index of 0.34.2 In the second study, which was a comparative trial of continuous LNG/EE and traditional cyclic LNG/EE in 641 women, only one pregnancy occurred in the continuous LNG/EE group and three pregnancies occurred in the cyclic LNG/EE group, which is statistically not a significant difference.3 Overall, the contraceptive efficacy of continuous LNG/EE was comparable to that of cyclic OC regimens.7

Effect on Menses

There is growing evidence that continuous contraceptive use of Lybrel may produce amenorrhea in women desiring to inhibit menses. The effect on menses was reported in two 1-year clinical studies in 2,134 healthy women aged 18 to 49. In the first open-label clinical study, 58.7% of women reported that they had achieved induced amenorrhea by pack 13 and 79% of women reported an absence of bleeding. However, most women experienced breakthrough bleeding or spotting during the first 3 to 6 months following continuous contraceptive use.2 In the second phase 3, multicenter, open-label study on a return to menses or fertility, it was reported that among the 187 women who discontinued the continuous LNG/EE regimen, 181 women reported a return to menses after a median of 32 days. Resumption to menses or fertility occurred within 30 days in 40.1% of women, within 60 days in 94.7% of women, and 90 days in 98.9% of women.

Likewise, an observational trial on the effect on menses, conducted by Teichmann et al. in 2006, reported that women achieved amenorrhea with time, with 27.1%, 39.6%, and 52.9% of women who were amenorrheic at packs 3, 7, and 13, respectively. A decrease in the incidence of breakthrough bleeding was reported in women by pack 4.3,5

Continuous contraceptive use effectively reduced amenorrhea in women in a randomized clinical trial. Women were randomized to either a cyclic (n=28) or a continuous use regimen (n=32). With women who were given a continuous use regimen 49%, 68%, and 88% reported no bleeding during cycles 2, 6, and 12, respectively. Thus, the percentage of women (88%) who achieved amenorrhea during cycles 10-12 for the continuous use
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regimen was significantly higher than that of the cyclic regimen. Spotting was present in women during cycles 1-21 but women reported a reduction with time.\textsuperscript{6,8}

A recent review comparing the continuous use regimen (> 28 days) with the cyclic use regimen (21-day regimen) of COCs, conducted by Edelman et al. in 2005, reported similar findings on bleeding patterns. Breakthrough bleeding or spotting was either improved or remained the same when compared to studies on traditional cyclic regimens.\textsuperscript{7}

Overall, the continuous LNG/EE regimen inhibits menses by induced amenorrhea and an absence of breakthrough bleeding over long-term use, as evidenced by the number of patients who achieved amenorrhea and by a reduction in the incidence of breakthrough bleeding with time. The continuous LNG/EE regimen does not have an effect on a return to menses or on a delay to fertility.\textsuperscript{5}


NEW PROGESTINS

New progestins include drospirenone (DRSP) and cyproterone acetate (CPA) and are highlighted below.

Drospirenone

DRSP, an analogue to spironolactone, is a synthetic progestin with progestogenic, antimineralocorticoid and antiandrogenic activities. The novel progestin DRSP is used in a COC containing 3 mg of DRSP and 20 mcg of EE (Yaz). Several studies have indicated that DRSP is used for the treatment of androgen-related disorders such as acne and hirsutism, and premenstrual dysphoric disorder (PMDD).\textsuperscript{1,3,6-8} Bleeding pattern, patient satisfaction and tolerance were assessed in 3,488 women in Europe, the Middle East and Canada in a multicenter, prospective study conducted by Endrikat et al. in 2009. Women receiving DRSP/EE showed beneficial effects to bleeding pattern, patient satisfaction and tolerance to the product.\textsuperscript{4} Case reports suggest that DRSP/EE might be associated with increased risk of VTE, but whether extended OC regimens or a reduction in the HFI increases the risk of VTE still remains to be determined.\textsuperscript{5}

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Cyproterone Acetate

Cyproterone acetate (CPA), a derivative of 17-hydroxyprogesterone, is a strong synthetic progestin and androgen receptor antagonist with weak gestational and glucocorticoid activity. CPA is available in Europe and Canada as a COC containing 2 mg CPA and 35 mcg EE (Dianette, Schering Health). Long-term use of CPA/EE has been associated with an increased risk for DVT. A recent review reported that VTE is no more common in CPA/EE than with that of third-generation COCs. On the contrary, a case-control study demonstrated that VTE increased four-fold in women using CPA/EE than that of COCs containing levonorgestrel. A nested cohort analysis and a case-control study demonstrated similar results, with VTE increasing significantly in women using combination CPA/EE.

Like DRSP, CPA has antiandrogenic properties and is used for the treatment of hirsutism and acne in hyperandrogenic women. Hirsutism is frequently a consequence of an excess of ovarian androgen production and has been associated with polycystic ovary syndrome (POS). Moderate acne was improved in healthy women between aged 16 and 45 in a randomized trial, proving to be a suitable option for the treatment of mild to moderate acne.


3. Palombo-Kinne E, Schellschmidt I, Schumacher U, Gräser T. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. Contraception 2009; 79:282-9
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CONCLUSION

Since the 1960s, OCs were administered in the traditional 21/7 cyclic regimen. Recent studies have reported that extended (24/4) and continuous-cycle regimens (84/7) are as effective in preventing ovulation and unintended pregnancy as traditional cyclic regimens. Extended- and continuous-cycle oral contraceptives remain a new option for reproductive aged women desiring fewer menstrual episodes per year or for those who desire to eliminate menstruation altogether. These new regimens also have similar adverse effects when compared to the standard 21/7 regimen, but differ in one respect: bleeding pattern.

Assessment on the effectiveness and safety profile demonstrate that these new products are comparable to that of 21/7 regimens and are an effective OC option. The emergence of a shortened HFI in contraceptive regimens such as 24/4 regimens (Seasonique and Loestrin 24 Fe), 84/7 regimens (Yaz), and Lybrel has decreased the risk of ovulation and unintended pregnancy and has further reduced symptoms associated with hormone withdrawal, particularly breakthrough bleeding and spotting. While a monthly withdrawal bleed may reassure some women that they are not pregnant, others prefer avoiding their monthly period and its associated attendant symptoms altogether. The new formulations offer women the ability to shorten the number of monthly withdrawal bleeds per year with products like Seasonique, Yaz, and Loestrin 24 Fe or should they prefer, eliminate menstruation completely with Lybrel. Extended and continuous-cycle OCs are useful in the treatment of hirsutism, PMDD, acne, and POS.

I also worked with Basic Health International and Reproductive Choice Service, both an integral part of the OB/GYN department at Bellevue Hospital. I observed pre-op, post-op, first trimester abortions (up to 9 weeks gestation) and second trimester abortions (up to 24 weeks gestation). Viewing first and second trimester abortions was a wonderful experience in this internship. I had the opportunity to engage in conversation with some of the patients and hear about their backgrounds, upbringing, or life situation. Lastly, I also had an opportunity to visit the nursery, which was an awesome experience.
In addition to my internship, I read a very moving book titled *Choice: True Stories of Birth, Contraception, Infertility, Adoption, Single Parenthood, & Abortion*. The book focused its attention on highlighting women and their struggles by documenting a story in their lives relating to reproductive choice. I strongly encourage everyone to read this inspirational and moving book because it really touched on a number of issues regarding women’s reproductive decisions and addressing the complexity of those decisions.

Furthermore, I participated in an interactive video on HPV that will serve as an educational module for future medical students and residents in the OB/GYN Department at Bellevue Hospital. I was asked by one of the administrative staff (Elizabeth who heads the medical students doing their rotations) in the OB/GYN department to lend a hand in creating a video focused around a doctor giving patient advice and answering questions from the concerned patient. After making the video, I found out that I really learned a lot about HPV and the some of the concerns that women have about it.

Other components of my internship consisted of doing administrative work for Reproductive Choice Service at Bellevue Hospital. I cannot count the number of discharge forms that I copied repeatedly for hours; however, I found it to be rewarding because I knew in the back of my mind that the work that I was doing was both meaningful and purposeful.

Overall, my experience working with Dr. Miriam Cremer and the OB/GYN department at Bellevue Hospital was two-fold. First, working with Dr. Cremer on the research project was something I found to be very rewarding and educational within the context and framework of women’s reproductive choice. Second, working with the administrative staff in the OB/GYN department at Bellevue Hospital, especially Elizabeth, really helped sharpened my
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awareness of women’s rights and reproductive choice. It also taught me a lot about the patients, all of who come from different socio-economic backgrounds.

I would recommend the internship to those who are looking at a career in being a doctor, like myself, and who also have a passion for learning about the intersections of women’s reproductive rights and social justice. As for recommendations for future RRASC interns, I would advise RRASCs to be punctual, respectful, communicative, personable, and receptive. These qualities are what I believe to be important in succeeding throughout this internship.