Psychosexual well-being in women using oral contraceptives containing drospirenone

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Summary

Considerable advances have been made in hormonal contraception in recent years, geared at maximizing compliance and minimizing discontinuation. In oral contraceptive (OC) formulations, the estrogenic component, generally ethinyl estradiol (EE), has been significantly reduced; in addition, new regimens (extended, flexible, 24/4 formats instead of the standard 21/7 format) and innovative delivery systems (vaginal rings, transdermal patches, subcutaneous implants and intrauterine devices) are available. The multitude of choices allows hormonal contraception to be tailored to the individual woman in order to obtain non-contraceptive benefits, without significant side effects, and also a favorable risk/benefit profile for her general and reproductive health.

Over the past few years, new OC formulations combining DRSP (3 mg), a unique progestin with both antimineralcorticoid and antiandrogenic activities, with estrogen (30 mcg or 20 mcg EE), in two regimens (24/4 and 21/7) of active pills in a 28-day cycle, have shown positive effects on water retention-related weight gain and physical, emotional and psychosexual well-being. It seems likely that the use of a low-dose, well-balanced OC and the shorter 4-day hormone-free interval may minimize the side effects that can impair quality of life and thus increase women’s compliance with hormonal contraception therapy.

KEY WORDS: drospirenone, oral contraceptives, premenstrual disorders, sexual function, 21/7 regimen, 24/4 regimen.

Introduction

Considerable advances have been made in hormonal contraception in recent years, geared at maximizing compliance and minimizing discontinuation. The aim of these innovations is to tailor hormonal contraception to the individual woman in order to obtain non-contraceptive benefits (improved skin, pelvic pain relief, cycle control, etc.), without significant side effects (nausea, water retention, weight gain, headaches, etc.), and also a favorable risk/benefit profile for her general and reproductive health.

Indeed, in oral contraceptive (OC) formulations, the estrogenic component, generally ethinyl estradiol (EE), has been significantly reduced and newer progestins, like dienogest and drospirenone (DRSP), two compounds with different molecular structures, have been introduced; in addition, new regimens (extended, flexible, 24/4 formats instead of the standard 21/7 format) and innovative delivery systems (vaginal rings, transdermal patches, subcutaneous implants and intrauterine devices) are available (1).

Despite the multitude of birth control options, oral contraceptives (OCs) remain the most common method of reversible contraception and have been proven to be useful in the treatment of a number of menstrually-related symptoms. However, not all women feel empowered by this choice of contraception; indeed, over the decades since the introduction of the OC pill reports have appeared which suggest a possible association with negative effects on mental well-being and sexual satisfaction, which may be major causes of poor compliance and unintended pregnancies. It is likely that some women, partly because of behavioural mistakes and misconceptions about the OC pill, fail to experience the physical, psychological and relational benefits (in terms of body image, reproductive health and family planning, eroticism and intimacy, working energy and quality of life) associated with OC use, and thus become ambivalent about or feel manipulated by “the pill” (2). Furthermore, the standard 7-day hormone-free interval may be a time of considerable distress for many women, due to the worsening of hormone-related symptoms during this withdrawal period compared with the 21 days of hormone-containing pills (3,4). In addition, the 7-day hormone-free interval in low-dose OCs is associated with reduced pituitary-ovarian suppression, which can allow ovarian follicular development, endogenous estradiol production, possible ovarian cyst formation and even ovulation (5).

In view of these considerations, we aimed to analyze critically the impact of OCs on psychosexual well-being in the light of the availability of new formulations containing DRSP (3 mg), a unique progestin with both antimineralcorticoid and antiandrogenic activities, which allow
two possible estrogen doses (30 mcg or 20 mcg EE) and two regimens (21/7 or 24/4) of active pills in a 28-day cycle.

**Peculiarities of drospirenone**

The synthetic progestins used in contraception and in menopausal hormone therapy show profound differences, which depend on their structure or metabolites. It is therefore inappropriate to consider the various effects of the old and new molecules as class effects. Indeed, while the progestogenic effect is common to all progestins, the biological effects of the various progestins vary widely and this variability has to be taken into account when considering the medical treatment of certain conditions; in addition, there may also occur specific side effects which can influence compliance (6,7).

Progestins are derived either from testosterone (19-nortestosterone derivatives) or from progesterone (17-OH progesterone derivatives and 19-norprogesterone derivatives). Among the 19-nortestosterone derivatives, the estrane group includes norethisterone and its metabolites, and the gonane group includes levonorgestrel (LNG) and its derivatives. The LNG derivatives, including desogestrel and its sub-derivatives etonogestrel, gestodene and norgestimate (norelgestromin), have been referred to as third-generation progestins. Several new progestins have been synthesized over the past decade and may be regarded as a fourth generation of progestins. Dienogest is referred to as a hybrid progestin, being derived from the estrane group with a 17alpha-cyanomethyl group, while DRSP derives from spiroloctane. These two progestins have no androgenic effect but do exert a partial antiandrogenic effect. Drospirenone (DRSP) is a unique progestin which exerts antimineralocorticoid effects and has a pharmacological profile almost identical to that of natural progesterone. In OC users, this property leads to decreased salt and water retention and a reduction of blood pressure. Indeed, EE tends to cause water retention, resulting in breast tenderness and feeling of bloating among some users of OCs. As DRSP 3 mg is equivalent to 25 mg of spironolactone, in the EE-DRSP combination this water retention is counteracted by a natriuretic effect, accordingly, decreases in both body weight and systolic and diastolic blood pressures were observed (8). The EE-DRSP combination may be as effective for mild to moderate acne as cyproterone acetate-containing OCs, and seems to relieve premenstrual syndrome (9,10). The results of a large multinational, prospective, non-interventional cohort study of new users of DRSP, LNG and other progestin-containing OCs, suggest that adverse cardiovascular and other serious events in users of a DRSP-containing OC are similar to those associated with the use of other OCs (11). Recently, a low-hormone version containing EE 20 mg and DRSP 3 mg has been marketed in two regimens: 21 and 24 days of active pills in a 28-day cycle (21/7 and 24/4 respectively). Like other DRSP-containing combined OCs, these low-dose regimens prevent water retention-related weight gain and improve physical and emotional well-being, and thus constitute an effective and well-tolerated choice of contraception with an acceptable bleeding pattern and a good safety profile (12). In addition, in two pivotal studies the 24/4 regimen was shown to be effective in treating the mood, physical and behavioral symptoms of premenstrual dysphoric disorder (PMDD) and symptoms specifically associated with food intake, water retention and negative interpersonal relationships. This effectiveness can probably be attributed to the shorter free interval and to the half-life (>30 hours) of DRSP, which continues to exert its activity well into the 4-day interval (13-15). Even though more evidence of the long-term effects of DRSP-containing pills is needed, there is no doubt that these formulations may be effective in women with severe premenstrual symptoms who wish to use OC for birth control, and in girls and women with moderate acne who are at least 14 years old, have reached menarche and wish to use OC for birth control (15,16).

**Psychosexual consequences of oral contraception**

There is a growing consensus that sexual health is an important aspect of well-being and quality of life in women and their partners across the entire reproductive life span. Women's sexuality is multidimensional, arising from a complex interplay of biological, psycho-relational and socio-cultural forces; critical reproductive events, including hormonal manipulations such as contraception during fertile life and replacement therapy at menopause, also affect sexual attitudes and behavior (17). The advent of hormonal contraception may be regarded as the greatest revolution in women's lives, allowing their sexuality to be separated from their reproductive capacity and allowing them to express their sexuality more freely without the fear of unwanted pregnancies.

Sex hormones modulate physical, emotional and cognitive components of the sexual response, affecting desire, mental and genital arousal, orgasm and satisfaction. Indeed, sex hormones modulate the cortical coordinating and controlling centers that are responsible for determining which sensations are to be perceived as sexual and for issuing appropriate commands to the rest of the nervous system. Sex hormones also affect the sensitivity thresholds of both non-genital and genital organs and, also of hypothalamic-limbic structures where, by influencing the release of specific neurotransmitters and neuromodulators, they elicit conscious perception and pleasurable reactions. Sex hormones, exerting peculiar effects at vascular, muscular and neural levels within the vulvar and vaginal tissues, play a critical role in the entire hemodynamic process leading to vasocongestion and lubrication (18). Pharmacological manipulations of sex hormones induce several neuroendocrine adaptive phenomena that involve a complex rearrangement of a vast array of neurotransmitters, neuromodulators and other neuroactive mediators of appetitive behaviors, pain threshold, mood and cognition. In addition to the specific effects on the hypothalamus and other reproduction-related brain areas, sex hormones are also involved in a multitude of non-reproductive brain functions. Therefore, any condition interfering with the normal neuroendocrine variations that occur across the menstrual cycle may induce a host of changes in brain function and behavior (19). Studies conducted in women of fertile age found an in-
increase in the establishment of interpersonal relationships and in pleasurable sexual exchanges during the periovulatory period, corresponding to the plasma androgenic peak, even though no clear correlation has been reported between plasma androgen levels and sexual response. The strong desire for sexual activity that coincides with the time of ovulation may also be related to the estradiol peak, which significantly contributes to arousal and lubrication (20-22). We very recently found a significant fluctuation of circulating oxytocin levels with a decline following ovulation, suggesting that this neuropeptide may influence the process of lubrication and genital responsiveness in the different phases of the menstrual cycle (23). The relationship between menstrual cyclicity and sexual behavior in humans is strongly complicated by the many factors that affect sexual motivation and response. These include physical and mental health throughout the menstrual cycle (including premenstrual disorders), lifestyle and work pressures (stress, weekend commitments), partner’s availability and desire, etc. (24-26).

The findings of studies dealing with the effects of OCs on sexuality are mixed due to the presence of some methodological limitations, the heterogeneity of the study populations, differences between hormonal contraceptive formulations, and changing attitudes to OC, and no consistent pattern of effects of OCs on sexual desire and response has therefore been demonstrated (27). In theory, OCs, being reliable and allowing increased sexual freedom, should exert a positive influence on sexuality. In addition, there may be indirect benefits linked to a more positive body image (due to better skin and hair condition) and to improved psychophysical performance (due to reduction of premenstrual symptoms, menstrual cramps and bleeding). A feeling of general well-being is an important factor in promoting intimacy and it contributes to sexual satisfaction. On the other hand, in some women, side effects, especially water retention and weight gain, mood swings and headache, unscheduled bleeding and spotting, may have a deleterious effect on sexual function by reducing the perception of quality of life across the menstrual cycle. Moreover, it is common in clinical practice to encounter women who report that they do not perceive changes in sexual awareness related to changes in sex hormone levels during the menstrual cycle. Sanders et al. (28) reported that emotional and sexual side effects, in particular worsening of premenstrual syndrome and decreased sexual arousability, were the best predictors of OC discontinuation-switching. Collectively, sexual side effects such as low libido, arousal disorders, lack of lubrication, dyspareunia and reduced sexual responsiveness have been attributed to the use of OCs and may reduce long-term compliance with these treatments. Some hormonal mechanisms have been hypothesized as possible causes of the side effects of OC. Indeed, the use of OCs significantly reduces ovarian and adrenal production of androgens, induces a significant reduction of bioavailable testosterone by increasing sex hormone binding globulin (SHBG), and lowers the activity of 5α-reductase in peripheral tissues. Similarly, there is a significant reduction in circulating estradiol levels because of reduced ovarian production, reduced conversion from precursors and higher binding due to the increase in circulating SHBG, which is also modulated by thyroid function, body weight, lifestyle, etc. (27,29).

Progestin type and estrogen/progestin ratio may also play a role in modulating sexual function and behavior, probably by differently affecting circulating androgens and the neural pathways involved in emotional well-being, including the opioidergic, GABAergic and serotoninergic systems (29). In addition, both in animal and in human studies, the modulatory effects of OC treatment on neuroactive steroids have been postulated to explain negative mood symptoms, but only in vulnerable subjects (30). Indeed, in healthy women with no underlying mood or anxiety disorder low-dose OCs did not induce adverse psychological symptoms in spite of significant reductions in neuroactive steroid levels (31). However, peculiar effects of different progestin types and doses combined with different EE doses may be hypothesized to explain the variety of central actions in OC users. Having said that, a large epidemiological study (32) found that OCs did not influence premenstrual mood in most women. Premenstrual mood is most likely to deteriorate in women with a history of depression and to improve in those with early-onset premenstrual mood disturbance or dysmenorrhea (32). Conversely, in another study conducted in premenopausal women with major depression, OC use was associated with less severe depressive symptoms, better overall physical function and a decreased number of comorbid anxiety disorders, findings that may be linked to the beneficial effects of ethinyl estradiol (33). Moreover, adolescents treated with OCs or placebo experienced similar numbers and types of OC side effects, as well as depressive symptoms (34). Collectively, these data on mood and affective behavior, like those on sexual function and behavior, are inconclusive, confirming the complexity of investigating subjective self-report symptoms under hormonal contraception therapy, which seems to be a unique experience in each individual woman.

In addition to the central effects of OCs on the main neuromodulatory systems involved in sexual desire and mood, peripherally, the lack of ovarian cyclicity during OC use, together with the reduced concentrations of sex hormones in vulvo-vaginal tissues, may induce marked changes in genital arousal and orgasmic response. The dose of EE, in particular, seems to play a critical role in inducing sexual dysfunction and favoring the development of vulvar vestibulitis syndrome in vulnerable women: a low-dose combination of EE (15 mcg) and gestodene was found to induce a decrease in sexual desire, excitement and pleasure over nine months of use (35). Indeed, some estrogen-dependent vascular and nerve remodeling phenomena have significant effects on vulvo-vaginal mucosa and smooth muscle, leading to changes in genital engorgement, lubrication and sensitivity. In spite of these extensive findings, the relationship between sexual function and sex hormone changes deriving from the use of OCs requires further exploration, especially in view of the fact that women on the pill with lower androgen levels were reported to declare a higher degree of sexual satisfaction (36). No correlation has been established between mean levels of testosterone and sexual desire, sexual interactions, or masturbation among contraceptive users, with only non-users reporting decreased sexual desire during the
perimenstrual period, in which there is a decrease in free testosterone (37). By contrast, during the pill-free week, when testosterone levels were found to be higher in contraceptive users in comparison with non-users, many women reported an increase in sexual motivation (38). Very recently, Graham et al. (39) demonstrated significant decreases in testosterone, free testosterone, and DHEA-S after three months of OC use, although the extent of the reduction was variable across women. Some evidence was found supporting a relationship between the degree of reduction in total and free testosterone and the frequency of sexual thoughts after three months. However, some women had no loss of sexual interest in spite of showing substantially reduced free testosterone levels, and there was, overall, no evidence that reduction in free testosterone affected enjoyment of sexual activity with a partner. These findings are consistent with the idea that some women may be more sensitive to changes in testosterone than others. No relationship was found between negative mood and changes in circulating androgens. In addition, the same authors, comparing two OC formulations, reported a considerable variability in mood changes, even though a greater improvement in premenstrual mood was evident in the young women using low-dose EE (25 mcg) OCs and showing less reduction of free testosterone. However, it is difficult to establish a causal relationship and further well-controlled studies are warranted (40).

Psychosexual well-being in women using DRSR-containing OCs

It has been established that when a woman's chosen method of contraception meets her expectations and she derives significant physical and psychological benefits from it, the long-term adherence with the therapy is quite high and its sexual side effects negligible. A large number of studies have shown that DRSR is a progestin with several receptor-mediated effects that considerably influence quality of life (41). As reported above, well-designed studies have shown that the use of DRSR-containing OCs not only offered cycle stabiility in both formulations (30 mcg and 20 mcg EE + 3 mg DRSR) without significantly affecting body weight, but also substantially improved premenstrual complaints, including PMDD, a more severe form of premenstrual syndrome characterized mainly by mental symptoms (42). A positive cosmetic effect has also been shown with a significant reduction of seborrhea and acne. It is also interesting to observe that young women using a pill containing 30 mcg EE + 3 mg DRSR reported an overall positive effect on sexual experience and behavior over nine months with a significant decrease of genital pain associated with intercourse during pill intake (43).

Collectively, these data strengthen the idea that use of a well-balanced OC, by minimizing the side effects that can impair quality of life, can maximize the potential health benefits of hormonal contraceptive treatment without having significantly negative consequences on the sexual attitudes and behavior of women choosing this form of birth control.

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