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Sex-hormone fluctuations and their effects on sexual function in IUS users

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Introduction

Unintended pregnancy affects many women's quality of life. Data suggest that unplanned pregnancies are a result of incorrect, inconsistent, or nonuse use of an effective contraceptive method (Smith, Jozkowski, & Sanders, 2014). A highly effective option for contraception is an intrauterine device, or IUD. The IUD is touted, by physicians and researchers alike, as one of the most effective methods for preventing pregnancy (AGOG). They are reversible, long-acting, and are increasingly considered a contraceptive method that can help lower the extremely high rate of unintended pregnancy in the United States which is currently hovering just below 50% (Finer & Zolna, 2011).

IUDs are a part of a group of contraceptive methods called LARCs or long-acting reversible contraception. A specific type of IUD that functions on a hormonal mechanism are called intrauterine systems or IUSs. LARCs are widely considered to be the most effective reversible contraceptive methods and include IUDs and the subdermal implant. LARC methods have been shown to have method failure rates close to tubal sterilization. IUDs have failure rates that are more in line with perfect use failure rates than with rates that account for human error (Stoddard, McNicholas, & Peipert, 2011). Unfortunately, few women in the United States are using IUDs (Stoddard, McNicholas, & Peipert, 2011). Despite being suggested as a first-line contraceptive method for women and adolescents (ACOG), only 5.5% of women in the United States who use contraceptives rely on IUDs as their primary method. This low rate is shocking when compared to the rest of the world where countries such as Norway and China have rates as high as 27% and 30% respectively (Gomez & Clark, 2014; Stoddard et al., 2011). When asked in 2002, as much as 39% of women in the United States reported not knowing anything about IUDs (Gomez & Clark, 2014; Stoddard et al., 2011). Because the United States is a nation with an extremely high incidence of unintended pregnancy, the lack of understanding regarding one of

the most effective forms of birth control is unsettling. The low use of IUDs in the United States can most likely be attributed to a lack of trained providers, high initial cost, and inaccurate knowledge both among clinicians and patients (Stoddard, McNicholas, & Peipert, 2011). According to Smith and colleagues (2014), "identifying the factors that may contribute to women's nonuse or inconsistent use of hormonal contraception is extremely important for the continued promotion of planned and timed pregnancies in the United States" (p. 469). One of the major factors that may contribute to nonuse, inconsistent use, or discontinuation of a method are the method's effects on sexual function. Women have reported that hormonal fluctuations and effects on sexual function as contributing factors to inconsistent or nonuse of a method (Sanders, Graham, Bass, Bancroft, 2001). There exists a plethora of literature on the effects of oral contraceptive pills (OCPs) on hormones and sexual function, but there is not a comparable amount of data on the effects of IUDs on the same parameters. The gap in the literature leads to the question: what is the effect of hormonal IUDs on hormone fluctuations and sexual function?

Answering the above question is imperative to improving knowledge around IUD usage. In order to reduce the number of unplanned pregnancies, strategies to improve consistent use of contraception by young women and teenagers must be determined. Because women who had heard about the IUD from a healthcare provider were 2.7 times more likely to be interested in using the method, enhancing knowledge and determining a strategy to improve consistent contraceptive use are linked (Fleming, Sokoloff, & Raine 2010). Clinicians should be knowledgeable about IUDs and encouraged to talk to women about them. To promote IUD use through conversation, providers must fully understand the side effects of IUDs including their effects on hormones and sexual function.

Literature Review

Unintended pregnancy and effective contraceptive methods to help women prevent pregnancy have be prevalent topics in public health literature. As such, a plethora of research has been established to determine the most effective methods of preventing pregnancy. Within the current literature, IUDs provide a notable contrast to most other reversible contraceptive methods such as the oral contraceptive pill (OCP) because they are more effective. Unlike OCPs, IUDs present no risk of failure due to error, poor adherence, or noncompliance (Anderson et al. 2014). As such, IUDs have efficacy rates close to those of tubal sterilization at less than 1%, while typical oral contraceptive efficacy rate is 8-9% (Stoddard, McNicholas, & Peipert, 2011). No attention is required on the part of an IUD user after insertion until time for removal, making IUDs a significantly more effective method than OCPs when considering user error.

Despite their efficacy, very few women in the United States use IUDs as their primary method of contraception. Rates for IUD usage among women in the United States who are practicing birth control hover around 5.5% (Stoddard, McNicholas, & Peipert, 2011). The low rate of IUD use in the United States is likely related to a number of factors; however, the most notable is lack of provider knowledge (Anderson et al. 2014). Because very little information exists on the effects of hormonal IUDs on sex-hormone levels and the subsequent effects on sexual function, providers cannot have appropriate conversations with women regarding IUDs and their sexual health. Lack of provider knowledge regarding IUDs and sexual function is important because sexual function is a primary reason that many women discontinue a contraceptive method. Sanders et al. (2014) found that, in a cohort of women using oral contraceptive pills, 8% of women who discontinued or switched pills did so because of sexual side effects. Women who are using or may be interested in using IUDs will have questions about potential sexual side effects that the devices may have. Additionally, women are more likely to

consider using an IUD if they hear about the method from their providers (Fleming, Sokoloff, & Raine 2010). Studies also indicate that providers who have access to more evidence-based information are significantly more likely to offer information about IUDs to their patients (Fleming, Sokoloff, & Raine 2010), demonstrating that providers need to be equipped with the knowledge to initiate conversations about IUDs; properly answer their patients' questions about IUDs, hormones, and sexual function; and address their patients' concerns regarding IUDs.

Although there is a lack of research surrounding hormonal IUDs, sex-hormone levels, and sexual function, there is a large amount of data covering oral contraceptive methods and their effects on hormones and sexual function. Understandably, more research has been done on hormone levels and sexual function in women taking oral contraceptives. Oral contraceptives are the most popular form of reversible contraception used in the United States with approximately 80% of women using oral contraceptives at some point in their lifetimes (Rosenberg, Waugh, 1998). However, because compliance is a major contributor to the lower effectiveness rate of oral contraceptives, more research should be done to level the playing field in the literature between IUDs and OCPs to equip clinicians and public health workers with the proper knowledge and abilities to properly address unintended pregnancy.

Given their hormonal nature, it is understandable that many researchers questioned, early on, the effects that oral contraceptives would have on hormones. In general, combined oral contraceptives decrease ovarian production of testosterone (Burrows, Basha, Goldstein 2012). because they inhibit luteinizing hormone (LH). The estrogen component of combined oral contraceptives leads to an increased production on sex hormone binding globulin (SHBG) which in turn decreases free testosterone and other androgens (Burrows, Basha, Goldstein 2012). New pills, especially, have been shown to significantly decrease free testosterone and increase SHBG

levels (Shah & Hoffstetter 2010). Studies centered around OCPs conclude that their effects on androgens specifically, can affect lubrication and potentially affect arousal and desire. In a study conducted by Wahin-Jocobsen and colleagues (2017), lower levels of free testosterone and androstenedione was associated with low sexual desire; however, the effect of a hormonal IUDs on testosterone and androstenedione levels is unknown. In one of the earliest studies done on modern combined oral contraceptives (COCs) and their effects on sexual function, women who were using oral contraceptives were significantly more likely to report decreased vaginal lubrication (Burrows, Basha, Goldstein 2012). The increase in reporting of vaginal dryness among oral contraceptive users may be explained by the fact that androgens are required for the early aspects of mucous formation (Burrows, Basha, Goldstein 2012). In a cross-sectional study of 349 pre- and postmenopausal women, Davison et al. (2008) found that women who were using or had used a COC were less likely than other women to report sexual thoughts and sexual interest. These women also reported fewer days of sexual activity per month than nonusers (Davison et al. 2008). Studies have also linked COCs to vestibular pain and have concluded that taking COCs may predispose women to vestibular pain. One study found that the likelihood of developing vestibulodynia was highest in women who had been taking the pill the longest and women who had begun taking the pill at a younger age (Burrows, Basha, Goldstein 2012). Literature also exists that explores the effects of Depot Medroxyprogesterone Acetate (DMPA) on sexual function. DMPA is a contraceptive method that is considered a monophasic method. DMPA is an injectable progestin (Burrows, Basha, Goldstein 2012). Like the IUD, DMPA is a LARC and provides reliable pregnancy prevention. Nelson (1996) found that around 5.8% of women who rely on DMPA as their contraceptive method report lost or decreased libdo; however other authors such as Fortenberry & Hansel (2011) found no difference in sexual desire

compared with nonusers, indicating that more research needs to be done to determine the effects of monophasic, hormonal methods such as the DMPA and the hormonal IUD.

The connection between hormonal IUDs and females' sex-hormone levels has not been established; however, the system under which hormonal IUDs function is well understood. Hormonal IUDs work based on the levonorgestrel intrauterine system. Levonorgestrel (LNG) is a synthetic progestin that thickens cervical mucus and inhibits sperm motility (Stoddard et al., 2011). hormonal IUDs, referred to as IUSs when talking specifically about the hormonal system, release very low doses of progestins at a constant, daily dose (Abou-Setta, Attia, Ibrahim 2013). The term, IUS is used to specify that the IUD, with is an al-encompassing term that includes non-hormonal and hormonal devices, that is being referred to functions on a hormonal system. There are several different IUSs that are currently available. They are Mirena, Kyleena, and Skyla. Each one releases a different daily dose of LNG into the uterine cavity; however, they are all constant and none exceed 20 micrograms per day (Abou-Setta, Attia, Ibrahim 2013). Although not in IUSs specifically, synthetic progestins, like LNG, have been shown to suppress sex drive. They have even been used to suppress sexual urges in men (Smith et al., 2014). The effects that the low dose progestins may have on naturally occurring hormone fluctuations and the subsequent effects on sexual function in women who use IUSs have not been established, however.

In conclusion, the IUS is an effective contraceptive system that can be used to reduce the stubbornly high rates of unintended pregnancy in the United States; however, little research exists to equip healthcare providers and promoters with knowledge surrounding IUS use, sex-hormone fluctuations, and sexual function. Women need their healthcare providers to initiate conversations around hormonal IUDs and practitioners need more information to feel confident

talking about hormonal IUDs (Fleming, Sokoloff, & Raine 2010). Research that has been done on OCP users suggests that synthetic hormones, including the progestins that are used in low doses in hormonal IUDs, affect naturally occurring hormone levels as well as sexual function (Burrows, Basha, Goldstein 2012). This study focused on hormonal fluctuations experienced by IUS users and the effects of various fluctuation levels on sexual function domains such as desire and lubrication which have been shown to be associated with hormone levels and hormonal contraceptive methods. The purpose of the study was to examine sex-hormone fluctuations in IUS users and sexual function in relation to the observed sex-hormone fluctuations in order to bridge the gap in literature surrounding IUSs.

Methods

Participants

This study consisted of women (N=19, aged 18 – 31 years) who had an IUD, referred to as IUS when talking specifically about hormonal IUDs, (Mirena, Skyla, or Kyleena) for at least 12 months prior to participation in the study. Participants were all within 80% - 130% of ideal body weight, had a regular sex partner, and were not taking any medications known to impact sexual function or sex hormones, such as SSRIs. The participants were all white women and had, on average, 3.88 sexual encounters (solitary and partnered) per week.

Procedures

Each participant initially reported to the lab for a screening meeting to ensure that she met the inclusion criteria for body weight (80%-130% of ideal body weight). At this initial visit, the participants also complete two surveys: a demographic survey and a survey that was also given at each subsequent visit. Additionally, participants provided a blood sample. After the initial visit, participants reported to the lab once per week for three additional weeks to have blood drawn and complete the survey. The survey measured sexual function by using the Female

Sexual Function Index (FSFI) (Rosen et al. 2000). The FSFI is a multidimensional instrument that assesses sexual function in the prior week based on self-reports (Rosen et al. 2000). It contains six domains; desire, arousal, lubrication, orgasm, satisfaction, and pain, and it is designed for females with a regular sex partners who experience sexual activity during the time period studied (Rosen et al. 2000). While completing the survey, participants were also engaging in a 15-minute sitting period to allow for blood volume to stabilize. After the survey and the sitting period were completed, the blood was collected using a 8.5 mL serum separating tube. The blood sample was allowed to clot for 20 minutes. After the clotting period, the blood was put into a centrifuge for 15 minutes at 2200 G and 20 degrees Celsius. When it was removed from the centrifuge, the serum had separated to a point where it was able to be removed and placed, evenly, into six cryotubes and frozen at -80 degrees Celsius. The serum remained frozen until later analysis.

After reaching nineteen participants with four data collections for each participant (once per week for four weeks), the serum was thawed for use in the enzyme-linked immunosorbent assays (ELISAs). Multiple ELISAs were run to measure the sex hormones present in the blood serum. The ELISA method provided readings on estradiol, progesterone, testosterone, and androstenedione. Data collection over a one-month time period helped to prevent many psychosocial variables from impacting results. All participants remained in steady relationships and were less likely to have a drastic change in their health or lives; therefore, the sexual function relationship, presumably, was to hormones specifically as compared to psychosocial variables.

Data Analysis

Data were analyzed using a linear mixed model in the R programming language using the lme4 package. When a significant relationship between hormone concentration and any measure of sexual function was detected follow-up pairwise comparisons were made using the emmeans package. After the data were analyzed in the R program, data were evaluated using an analysis of variance (ANOVA). An ANOVA was run on each outcome variable from the FSFI (arousal, satisfaction, lubrication, desire, and orgasm) as the dependent variable and hormone levels (testosterone, estradiol, progesterone, and androstenedione) as the independent variable. When a significant ANOVA effect was detected, pairwise comparisons were conducted. Significance was set at an alpha of less than .05. Marginal significance was set at an alpha of less than .051 to .09.

Results

There were no significant associations between testosterone and the outcome variables: arousal [$F(2.25,24.79)=0.62$, $p = .56$], satisfaction [$F(2.40,26.44)=0.19$, $p = .86$], lubrication [$F(2.08,22.86)=0.29$, $p = .76$], desire [$F(2.35,25.87)=0.14$, $p = .90$], or orgasm [$F(2.49,27.36)=0.71$, $p = .53$]. There were also no significant associations between estradiol and the outcome variables: arousal [$F(2.37,42.59)=0.63$, $p = .56$], satisfaction [$F(2.44,43.96)=0.93$, $p = .42$], lubrication [$F(2.55,45.86)=0.14$, $p = .92$], desire [$F(2.45,44.04)=0.51$, $p = .64$], or orgasm [$F(2.70,48.56)=0.42$, $p = .72$]. Additionally, there were no significant associations between progesterone and the outcome variables: arousal [$F(2.11,29.59)=1.47$, $p = .25$], satisfaction [$F(2.60,36.44)=0.70$, $p = .54$], lubrication [$F(2.26,31.65)=1.06$, $p = .37$], desire [$F(1.86,26.07)=1.26$, $p = .30$], or orgasm [$F(2.61,36.59)=0.64$, $p = .57$]. Androstenedione had a significant association with changes in vaginal lubrication [$F(1.77,31.92)=5.96$, $p = .008$], and a marginally significant association with fluctuations in arousal [$F(2.13,38.29)=3.00$, $p = .06$] and

orgasm [F(1.96,35.29)=3.14, p = .06]. Androstenedione had no association with satisfaction [F(2.61,47.02)=1.02, p = .39] or desire [F(2.40,43.24)=1.30, p = .29].

Discussion

The current study hypothesized that there would be an association between varying levels of androstenedione and sexual function, specifically lubrication: as androstenedione increased, it was expected that lubrication and the other sexual function outcome variables would also increase. The study also hypothesized that as progesterone increased, sexual function would decrease and that there would be no association between estradiol and testosterone and sexual function. Literature points toward an association between androgens and sexual function in OCP users (Burrows, Basha, Goldstein 2012); however, the directionality of the relationship is ambiguous for estradiol and testosterone. Additionally, the study hypothesized that IUS users would experience sex-hormone fluctuations despite the constant, daily, low dose of LNG released into the uterine cavity each day over the course of their IUS use (Abou-Setta, Attia, Ibrahim 2013). The null hypothesis for all associations was that there would be no association; therefore, for androstenedione, the null hypothesis was rejected and for all other sex-hormones, the null hypotheses failed to be rejected.

Although the null hypothesis for androstenedione was rejected, the outcome was slightly different than expected. The increase in androstenedione did lead to a subsequent increase in several sexual function domains (lubrication, desire, arousal, and orgasm); however, the data for androstenedione followed a cubic relationship meaning that at a certain point, an increase in androstenedione led to decreased sexual function domains. For IUS users, this might mean that if they are more sensitive to variations in androstenedione, they could experience varying sexual function effects.

The relationship between androstenedione and sexual function is important because it can be used to better inform potential IUS users on side effects as well as help clinicians and women make decisions on what methods are best considering their reactions to androstenedione fluctuations. Better informing clinicians and women on effective contraceptive methods will potentially help to reduce the number of unintended pregnancies by making both the prescribers and the users feel more confident in their methods. It may also contribute to consistent, continued use of IUSs because the side effects will be better understood. Additionally, the fact that many of the hormone fluctuations experienced by IUS users were not associated with sexual function can also be used to help better inform potential users. Because many women have reported hormonal fluctuations and effects on sexual function as contributing factors to inconsistent or nonuse of a method, being able to understand specific effects on sexual function will be important in promoting consistent use. (Sanders, Graham, Bass, Bancroft, 2001). If clinicians are able to confidently tell women that their sexual function should not be affected or are able to tell women how their sexual function will be affected, more women may choose to use an IUS, ultimately helping to reduce numbers of unintended pregnancies.

In comparison to the research conducted on OCPs and sexual function, the results from this study suggest that IUS users experience fewer changes in sexual function. Given the prevalence of negative sexual function effects of OCPs, the IUS may be a preferable choice for women who have experienced negative effects during OCP use. Physicians are encouraged to discuss sexual side effects of all contraceptive options with patients, along with other effects, to provide the most comprehensive information for patients in their decisions about contraceptive methods.

Limitations

As one of the first studies to assess the effects of IUS on sexual function, this study contributes to the literature and knowledge on this topic, but is not exempt from limitations such as a small sample size, the limited time frame (4 weeks), and the inconsistency in some participants experiencing a menses while others did not during that time frame. Further research is needed to better understand the long term associations of IUS use with sexual function, including with a larger, more diverse sample of women, who have been using the systems for various amounts of time. Future research should aim to compare different IUS brands (e.g., Mirena, Skyla, Liletta, etc.), particularly those that may have differing amounts of LNG. Additionally, further research is needed to specifically compare IUS users and nonusers to better associate the hormone fluctuations and sexual function with the IUS.

Tables and Figures

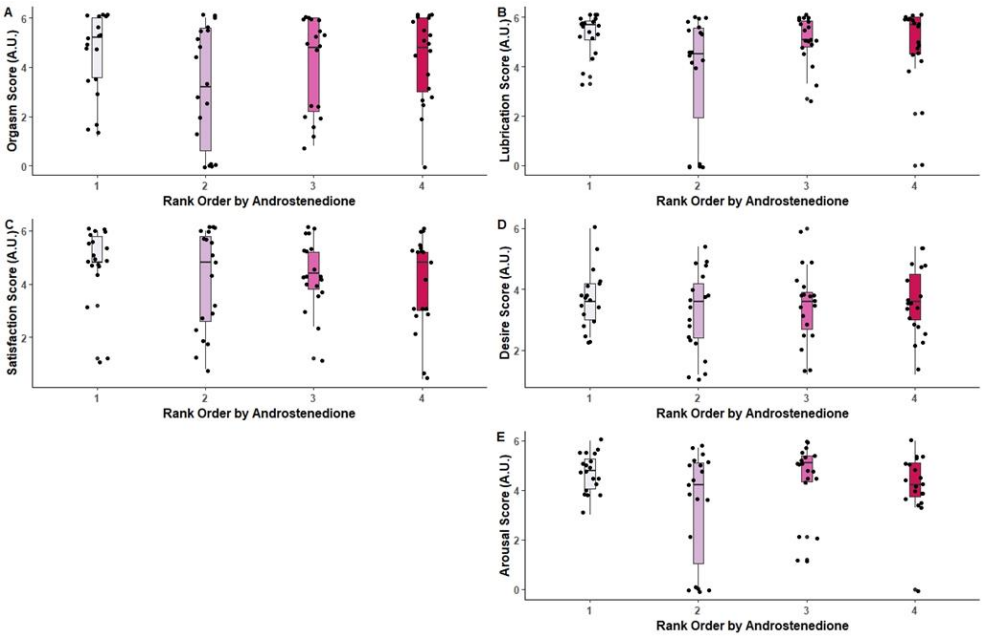

***Figure 2*:** Five of the FSFI subscale scores presented from the week with the lowest androstenedione levels to the highest level of androstenedione levels

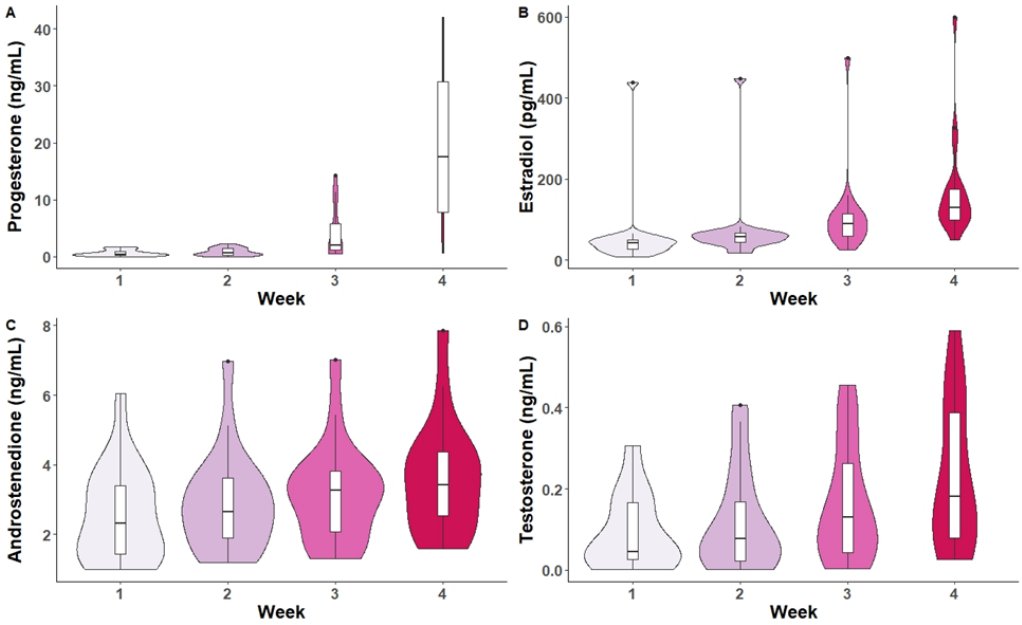

***Figure 1*:** Rank-ordered from lowest to highest hormone levels of participants throughout each week of the study. The labeling does not correspond with the data collection (i.e. Week 1 does not equal visit 1).

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