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Editorial Commentary: Beyond "Users" and "Non-Users": Insights from a Murine Model of Oral Contraceptive Formulations

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Oral contraceptive pills (OCP) are a commonly prescribed medication in the United States and worldwide for female individuals in the athletic and general populations. Research often compares female participants as oral contraceptive pill "users" or "non-users." However, there are distinct types of oral contraceptives with differences in synthetic hormones and doses. The heterogeneity in hormone type and dosage composition represents a critical variable when investigating the impact of oral contraceptive pills on musculoskeletal health and athletic performance. Many athletes are opting to use OCPs to manipulate their menstrual cycles in coordination with training and competition schedules. Just as it is important to understand how different OCPs affect menstrual patterns to guide individualized prescribing, so too should we strive to understand their musculoskeletal effects. Improved knowledge in this area will allow clinicians to optimize OCP prescription to further support musculoskeletal health and performance.

Oral contraceptive pills are a commonly prescribed medication in the United States and worldwide for female individuals in the athletic and general populations. Research often compares female participants as oral contraceptive pill "users" or "non-users." However, there are distinct types of oral contraceptives with differences in synthetic hormones and doses. The heterogeneity in hormone type and dosage composition represents a critical variable when investigating the impact of oral contraceptive pills on musculoskeletal health and athletic performance. This study by Rau *et al.*[1] details a mouse model of oral intake of (1) no exogenous hormones, (2) a low estrogenic and high androgenic formulation, or (3) a high estrogenic and low androgenic formulation to evaluate differences in anthropometrics and estrous cycling, the murine analog for the human menstrual cycle. Their findings reveal that varying oral contraceptive formulations may disrupt the menstrual cycle in distinct ways. This work represents an important step in considering the systemic effects of different oral contraceptive pill compositions. As many athletes are selecting oral contraceptive pills based on how they modify the menstrual cycle and side effect profiles, improved knowledge in this area will allow clinicians to optimize oral contraceptive prescription to further support athletic performance.

Oral contraceptives pills (OCPs) represent the most commonly prescribed form of contraception in the United States.[2] Approximately 14% of female individuals ages 15-49 years old in the United States and more than 150 million female individuals worldwide use OCPs.[2, 3] Among athletes, OCP use has been reported to be similar or higher to that of the general population.[4, 5] In a study of 430 elite female athletes, Martin *et al.* found that 49.5% were currently using hormonal contraceptives and 69.8% had used hormonal contraceptives during their lifetime, with OCPs being the most commonly used form at 78.4%.[5] Though often discussed and

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researched as a homogenous class, these medications in fact comprise distinct categories, each characterized by unique properties and effects. One major distinguishing feature is that OCPs may be synthetic progestin-only or combined oral contraceptives (COCs), which include a combination of a synthetic estrogen and progestin. Within these types, the specific synthetic hormones and their dosages mayd also vary. While most formulations contain the synthetic estrogen ethinyl estradiol, the dosage is inconsistent. There is also substantial variability in the progestins used. This is of particular importance as progestins possess differing levels of androgenicity (i.e., degree of androgenic activity).[6, 7] Additionally, OCPs may be monophasic (stable amount of hormones in active pills) or multi-phasic (varying amounts of hormones in active pills). Collectively, these medications have great variability in hormone and dosage.

While better defining the hormonal impact of these medications is an essential step, understanding their musculoskeletal effects is also an important consideration given the high prevalence of use among athletes and building evidence that sex hormones may account for sex-based disparities in injuries.[4, 5, 8] This is exemplified by the investigations into if OCPs may be protective for female athletes in regards to anterior cruciate ligament (ACL) injuries.[9] As the interest in the impact of OCPs on musculoskeletal health and performance has increased, so has the quantity of research efforts. However, despite the growing body of literature, there is a lack of consensus on many of the systemic impacts of OCPs given inconsistent findings.[4, 10] A major limitation in this body of work is rooted in the methodology, with a tendency to broadly categorize female individuals as either "oral contraceptive users" or "non-users", without differentiating between formulations. This binary approach does not account for variation in synthetic hormone systemic effects or side effect profiles and likely obscures the true differences in outcomes. As such, the heterogeneity in hormone type and dosage composition represents a critical variable when investigating the impact of OCPs on musculoskeletal health and athletic performance.

In their study, Mouse Model for Combined Oral Contraceptive Administration in Diet, Rau et al developed a mouse model of oral intake of (1) no exogenous hormones, (2) a low estrogenic and high androgenic formulation, or (3) a high estrogenic and low androgenic formulation to evaluate differences in anthropometrics and estrous cycling, the murine analog for the human menstrual cycle. The formulations tested–low ethinyl estradiol and levonorgestrel (high androgenicty) and high ethinyl estradiol and desogestrel (low androgenicity)—represent commonly prescribed COCs. Both exogenous hormone formulations altered the estrous cycling, though in different ways. The high ethinyl estradiol and desogestrel resulted in a longer metestrus stage, the murine equivalent of the human early secretory phase when progesterone levels begin to rise.[11] In contrast, low ethinyl estradiol and levonorgestrel resulted in a longer diestrus stage, the murine equivalent of the human late secretory stage characterized by decreasing progesterone.[11] These findings highlight that not all COCs disrupt the menstrual cycle in the same way. There were no differences in duration of proestrus or estrus stages, which corresponds best to the ovulatory and luteal (mid secretory) phases of the human menstrual cycle, with hormonal peaks.[11] Serum estradiol levels, serum progesterone levels, and body weight changes were similar between all groups, providing greater insight into how different COCs may, or may not, impact circulating hormones. Anecdotally, the authors observed that mice in the low ethinyl estradiol and levonorgestrel group exhibited more squeaking and attempts to escape when restrained compared to the high ethinyl estradiol and desogestrel group. This, authors described, may be further evidence of systemic effects of exogenous hormones.

This research highlights the varying systemic effects of different OCP formulations. As demonstrated in this study, two COCs may produce different physiologic profiles, which underscores the need for more precise categorization of research participants and OCP use in future studies. Future work should aim to not only compare between groups that do and not use OCPs, but also to understand potentially distinctive effects among those using OCPs to assess for differences in progestin-only OCPs as well as COCs of high and low estrogenic and androgenic formulations. Consideration should also be made for the temporal aspect of testing if assessing multiphasic formulations.

Another important contribution of this work is the development of a murine model to investigate exogenous hormone intake on systemic hormones and the reproductive cycle, which can be manipulated to research musculoskeletal health. This model provides an important preclinical

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platform for future studies. The ability to investigate these effects allows further analysis into OCPs beyond the binary "users" and "non-users" and can be replicated to further determine how varying OCPs may impact musculoskeletal health. Such mechanistic insights can inform the design of clinical research to guide sports medicine physicians in tailoring contraceptive counseling for athletes.

Many athletes are opting to use OCPs to manipulate their menstrual cycles in coordination with training and competition schedules. For athletes, OCP selection is often influenced by known side effect profiles, particularly regarding cycle frequency and amount of withdrawal bleeding.[5] Just as it is important to understand how different OCPs affect menstrual patterns to guide individualized prescribing, so too should we strive to understand their musculoskeletal effects. This work by Rau *et al*. is an important step in comparing systemic effects of different OCPs. Improved knowledge in this area will allow clinicians to optimize OCP prescription to further support musculoskeletal health and performance.

Conflict of Interest Statement

The authors declare no conflicts of interest with the contents of this study.

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