Progestins and acne vulgaris: a review

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Abstract

The role of exogenous progestin in the development of acne is unclear. Progestins are known for their androgenic potential, but newer generations of progestins have low or anti-androgenic activity. This review will evaluate the association between progestins found in hormonal long-acting reversible contraceptives (intrauterine devices and subdermal implants) and acne, as well as the role of oral contraceptives in acne management. Our review demonstrates that the cause and effect relationship between progestins and acne is difficult to establish and future studies that seek to understand how progestins modulate acne are necessary.

Keywords: progestin, progesterone, acne, long acting reversible contraception, implant, intrauterine device, IUD, Nexplanon

Introduction

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit characterized by open and closed comedones and inflammatory lesions (papules, pustules, nodules, or cysts). In the United States, 85% of individuals aged 12-24 years are affected by acne [1]. Acne is associated with depression and anxiety, and has a significant impact on quality of life [2]. The factors involved in acne pathogenesis include androgen-induced elevated sebum secretion, perifollicular inflammation, and *Propionibacterium acnes* (*P. acnes*) colonization of the pilosebaceous unit [3]. Testosterone and dihydrotestosterone are the most powerful androgens implicated in acne development [4]. Within the pilosebaceous unit, weak androgen dihydroepiandrosterone sulfate (DHEA-S) is converted to testosterone and dihydrotestosterone, and testosterone to dihydrotestosterone (via 5-alpha reductase) [5]. Androgens and end-organ androgen receptor sensitivity are believed to be responsible for elevated sebum secretion. The goal of hormonal acne treatment is to minimize the effects of intrinsic androgens on the pilosebaceous unit through androgen receptor blockade, modification of the intrinsic androgenic effect, and inhibition of 5-alpha reductase in the adnexa. Hormonal contraceptives have varying capacity in their ability to affect these targets.

Many progestins are known for their intrinsic androgenic activity. However, newer, second generation progestins, such as norgestrel and levonorgestrel, have low androgenic potential [6]. Furthermore, third generation progestins, such as desogestrel and norgestimate, are even less androgenic. Drospirenone, cyproterone acetate, and dinogest have no intrinsic androgen effect and can actually block the androgen receptor [6-8]. Owing to variable androgenic potency, progestins may have variable effects on acne vulgaris. The purpose of this review is to evaluate the association between progestins found in hormonal long-acting reversible contraception methods (**Table 1**) and acne. We also briefly discuss oral contraceptives and their role in acne management.

Table 1. *Summary of the various progestins and birth control methods; long acting reversible contraceptive and oral contraceptive pill.*

	Long acting reversible contraception		
Progestin	Hormonal IUD	Subdermal Implant	OCP
Levonorgestrel (LNG)	X	X	X
Norgestrel			X
Desogestrel (DSG)			X
Etonogestrel (ETN)		X	X
Norgestimate			X
Chlormadinone acetate (CMA)			X
Drospirenone (DRSP)			X
Ciproterone acetate (CPA)			X
Dienogest (DG)			X
Norethindrone			X

IUD, intrauterine device; OCP, Oral Contraceptive Pill.

Body of Article

Long-acting reversible contraception methods

Long-acting reversible contraception methods include the intrauterine device (IUD) and the subdermal contraceptive implant. These methods are inserted by a trained clinician, last for several years, and can be removed at any time.

Intrauterine Devices: An Overview

Intrauterine devices (IUDs) were initially developed to provide an effective, but more localized, form of contraception for women seeking birth control. They are currently one of the most reliable and cost effective contraception methods on the market. Approximately 12 percent of women in the United States utilize intrauterine device contraception and this number has been rising in recent years [9]. In the United States, there are two major classes of IUDs, which include copper devices and levonorgestrel-containing devices. The TCu380A is the only FDA-approved copper IUD device, whereas there are four approved hormonal IUDs, including Mirena®, Liletta®, Kyleena®, and Skyla® [10].

Intrauterine Devices and Acne Vulgaris

There are currently no randomized controlled clinical trials specifically evaluating the effects of intrauterine devices on acne vulgaris. Limitations of current published studies include failure to assess forms of contraception used prior to IUD insertion and are limited to patient reported data. Since copper-based IUDs lack a direct hormonal component, the focus of this discussion and analysis will be the effect of levonorgestrel-containing IUDs on acne vulgaris (**Table 2**).

Table 2. *Levonorgestrel-IUDs by trade name and total/daily release dosages.*

IUD by Tradename	Dosage of Levonorgestrel (progestin)
Mirena®	52 mg total—released at 20ug/day for 5 years
Liletta®	52 mg total- avg of 15.6 ug/day released over three years
Skyla®	13.5 mg total- avg of 6 ug/day released over three years
Kyleena®	19.5 mg total- avg of 9 ug/day released over five years

IUD, intrauterine device.

Although progesterones are often categorized into different levels of androgenicity, direct effects of exogenous progesterone on acne development remains debated [11, 12]. The effects of progesterone in an IUD are believed to be local, but systemic hormonally related effects, including acne vulgaris, have been reported in the literature. In addition to its presence in IUDs, levonorgestrel is also found in combination oral contraceptive pills that have been shown to decrease acne counts. However, a number of studies evaluating the acceptability and efficacy of intrauterine devices and reviews on the same subject matter have reported acne as a side effect.

A randomized trial comparing Nova-T IUDs (copper-releasing IUD) with levonorgestrel-releasing IUDs (20µg/day) reported significantly ($P<0.001$) higher cumulative 60-month gross termination rates related to patient-reported acne in levonorgestrel-IUD users compared to Nova-T users (0.4 versus 2.3), [13].

A French clinical study of 203 women published in 2002 cited acne as one of the three major reasons for deliberate premature removal of the Mirena® (20µg/day release) IUD. The reported rate of acne was 1% in their study population [14].

A study by Nilsson and colleagues comparing the performance of two levonorgestrel-IUDs with the Nova-T copper device also reported higher rates of acne in women using the levonorgestrel-IUD devices. Specifically, within the first year of use, 16-17% of study subjects using two types of levonorgestrel-IUDs (one with a 20µg levonorgestrel daily release and the other with a 30µg levonorgestrel daily release) reported an increase in acne vulgaris lesions compared with 7.2% of Nova-T users (P <0.025). There was no statistically significant difference between the two levonorgestrel-IUD groups [15].

A large study (2147 patients) evaluating patient-reported rates of acne vulgaris with the use of different hormonal contraceptive methods noted a significant (P<0.001) worsening of acne vulgaris in patients utilizing hormonal intrauterine devices when compared to patients using vaginal rings and combined oral contraceptives [16].

There are also a few case reports in the literature describing acne vulgaris flares in women shortly after levonorgestrel-IUD placement. This includes a Dutch report of 2 women who developed severe acne within several weeks of levonorgestrel-IUD placement [17]. Another 5 cases of IUD-related acne vulgaris flares were reported in 2008 in five women on the back and/or jaw line after one-to-three months of levonorgestrel-IUD contraception [18].

All the studies above favor levonorgestrel-IUDs causing a flare of acne vulgaris. Limitations to the studies are that they are unclear if the different study arms had varying rates of cessation of oral contraceptives prior to the levonorgestrel-IUD being inserted, effectively removing the suppressive effects of the COC on acne. Additionally, the studies are lacking objective acne grading assessments and rely on patient surveys. Currently reported data on the effects of hormonal IUDs on acne have only focused on Mirena® IUDs, which are 20µg/day release formulations. Lower dose formulations such as Liletta®, Skyla®, or Kyleena® have not been studied in this context. Hypothetically, since these devices release a lower daily dose of progesterone, they may be less likely to induce systemic hormonal side effects, such as acne.

Subdermal Implant: An Overview

Nexplanon® is a subcutaneous contraceptive implant device that consists of 68mg etonogestrel and provides contraceptive coverage for up to three years. Nexplanon replaced Implanon (previous version of the device) as 50% of unintended pregnancies on Implanon were likely related to incorrect insertion technique or expulsion of the implant [19]. Nexplanon comes with a new applicator meant to resolve the problems encountered with Implanon. Nexplanon is a highly effective and reversible long acting reversible contraceptive, providing greater than 99% contraceptive protection [20].

Jadelle is a levonorgestrel containing implant that consists of two rods and lasts for up to five years. Similarly, Sino-Implant II is a two-rod levonorgestrel containing implant that lasts up to 4 years.

Subdermal Implant and Acne Vulgaris

Research into the effects of sub dermal implants is scant. As is seen with the IUD studies, authors do not report the birth control method used immediately prior to study enrollment, which could potentially have an impact on acne. Further randomized controlled trial with objective acne measures are needed to evaluate the effects of contraceptive implants on acne vulgaris.

A three-year randomized controlled trial of etonogestrel- (n=995) and levonorgestrel-releasing (n=997) contraceptive implants with non-randomized matched copper IUD (n=971) controls was conducted to investigate the side effects typically attributed to progestin-only methods, including acne vulgaris [21]. Follow up occurred at two weeks, three and 6 months, and semi-annually for three years or until pregnancy or method discontinuation. Subjective acne reports were recorded at follow up visits. Among subjects using etonogestrel implant, 45% reported acne during one or more follow up visits, compared to 42% in levonorgestrel group, showing no significant difference between the two methods (P=0.22). Although 32% of copper IUD users reported acne, this was significantly lower compared to the 44% acne rate when etonogestrel and levonorgestrel groups were combined (P<0.05). Although acne was

more common in implant users, it is striking that 32% of non-hormonal IUD users also reported acne. One significant flaw in this study is lack of baseline acne assessments and objective acne grading.

Oral Contraceptives: An Overview

Oral contraceptives come in two different formulations: as combined oral contraceptives (COCs) or progestin-only pills. Since unopposed estrogen is associated with endometrial cancer, COCs combine estrogen and progestin hormones to minimize the risk. Oral contraceptives lead to a reduction of free testosterone by suppressing ovarian steroid production and increasing the sex hormone binding globulin [22, 23]. Oral contraceptives also reduce dihydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS), [24]. Since androgens have been implicated in the development of acne, it would be reasonable to conclude that these hormonal changes might have an impact on acne vulgaris.

The Role of Progestins in Oral Contraceptives

There are no specific studies evaluating the rates of acne in progestin-only pills. Although progestins are known for their intrinsic androgenic activity, newer progestins have lower androgenic potential and some even have anti-androgenic effects in the sebaceous gland. Progestins used in long acting reversible contraceptives include levonorgestrel or etonorgestrel (etonogestrel). Progestins found in COC may include levonorgestrel, desogestrel, norgestimate, norethindrone, drospirenone, norgestrel, cyproterone acetate, or dinogest. Cyproterone acetate is used for acne treatment in Europe and Canada, but it is not approved in the United States [25].

Oral Contraceptive Progestins and Acne

Although all oral contraceptives are equally effective in preventing pregnancy if taken as directed, the Food and Drug Administration (FDA) has approved only three oral contraceptives for the treatment of acne vulgaris. Current research does not support their superiority in acne treatment over other forms of COCs. All three formulations combine estrogen (ethynyl estradiol) and a progestin hormone (either norgestimate, norethindrone, or drospirenone), (**Table 3**). To our knowledge, there are no studies on progestin-only pills and the development of acne. Based on a 2012 Cohrane review, clinician assessments and patient self-assessments of acne revealed that COCs largely had a similar effectiveness regardless of the progesterone utilized [12].

Table 3. *Subdermal contraceptive implants by trade name, progestin dosage, and period of contraception.*

Subdermal Implant by Tradename	Dosage of progestin	Period of contraception
Implanon®*	68 mg Etonogestrel (one rod)	3 years
Nexplanon®	68 mg Etonogestrel (one rod)	3 years
Jadelle®	75 mg each Levonorgestrel (two rods)	5 years
Sino-Implant II**	75 mg each Levonorgestrel (two rods)	4 years

*Implanon has been completely replaced by Nexplanon.
**Manufactured in China.

Specifically, the review analyzed data from nine placebo-controlled trials investigating the efficacy of six different COCs on acne lesion reduction. The COCs each contained one of the following progestins: levonorgestrel, norethindrone, norgestimate, drospirenone, dienogest, or chlormadinone acetate. The results showed that all six COCs, and therefore all six different progestins, were effective in reducing inflammatory and non-inflammatory acne lesions counts. However, owing to limited data it was not possible to compare the effectiveness of each progestin type on acne lesion counts. Few important differences were found between the different types of progestins. The authors did conclude that chlormadinone acetate or cyproterone acetate had a better effect on acne lesions than levonorgestrel and that cyproterone acetate was better than desogestrel but there were conflicting results. Levonorgestrel was slightly more effective than desogestrel but results were inconsistent. Drospirenone was more effective than norgestimate, but less effective than cyproterone acetate. Similarly to the Cochrane review, a recent review by Trivedi et al. concluded that COC use led to

Table 4. *Estrogen and progestin in FDA-approved oral contraceptives (OCs) for acne treatment listed by trade name and dosage of estrogen and progestin.I*

Oral contraceptive	Dosage of estrogen (mcg)	Dosage of progestin (mcg)
Ortho Tri-Cyclen	Ethynyl estradiol, 35	Norgestimate, 180, 215, 250
Estrostep	Ethynyl estradiol, 20, 30, 35	Norethindrone, 1000
Yaz, Loryna	Ethynyl estradiol, 20	Drospirenone, 3000

a significant decrease in acne lesions, with no consistent differences in efficacy between the various hormonal formulations [26].

A 2016 retrospective analysis of 2147 acne patients showed that COCs and vaginal ring, which also contains a combination of estrogen and progestin, improved acne, whereas progestin-only methods (DepoProvera injection, subdermal implant, and hormonal IUD) worsened acne. Drospirenone, a partial androgen blocker, was the most helpful progestin, followed by norgestimate and desogestrel; levonorgestreal and norethindrone were least helpful ($P<0.04$ for all pairwise comparisons). COCs with triphasic progestin provided the most benefit ($P<0.05$). Estrogen variation, on the other hand, did not have a significant impact on acne vulgaris ($P=0.9$), [16].

Although COCs have been shown to be effective in treating acne, there is no data to support the efficacy of COCs over other acne treatment modalities. In a meta-analysis of 14 studies on COCs, it was demonstrated that individuals using COCs had three times increased odds for developing venous thromboembolism compared to those not on COCs [27]. However, this risk is still lower than that experienced during pregnancy. The increased risk of deep vein thrombosis while using an oral contraceptive for acne alone needs to be discussed with the patient. Other progesterone related side effects might include nausea, vomiting, headache, bloating, breast tenderness, and weight changes.

Conclusion

Androgens are implicated in excess sebum production and acne pathogenesis. Some progestins have intrinsic androgenic properties and are therefore implicated in acne development. The newer progestins (e.g. desogestrel) have lower androgenic potential whereas others act as anti-androgens (e.g. drospirenone). Although studies report acne as a reason for long acting reversible contraceptive discontinuation, none of the studies report the birth control method subjects used immediately prior to study enrollment. It is notable that equivalent classes/generations of progesterone used in COCs are found to decrease acne vulgaris. Also, there are no studies on acne and progesterone only pills. Additionally, the majority of studies evaluating exogenous progestin effects on acne have no objective patient evaluation data. Therefore, the cause and effect relationship between progestins found in long acting reversible contraceptives and acne are difficult to establish. On the other hand, we know that levonorgestrel and etonogestrel have androgenic potential (levonorgestrel is more androgenic compared to etonogestrel), thus their systemic effect could impact the sebaceous gland to secrete more sebum, potentially elevating the risk for acne. The specific effects on the sebaceous gland of each of the progestins within equivalent classes may be different and should be the focus of future studies that seek to understand how progestins modulate acne. Studies that evaluate the role of starting long acting reversible contraceptives without a transition from oral contraceptive pills to long acting reversible contraceptives and objective acne grading data will be needed to better identify the association.

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