



Review

Comprehensive review of reports of menstrual irregularities associated with isotretinoin



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ABSTRACT

In 1982, oral isotretinoin was first licensed as a treatment option for severe recalcitrant cystic acne in the United States. Since its introduction into the pharmaceutical market, several instances of amenorrhea in women of child-bearing age taking isotretinoin have been reported. In each documented instance, amenorrhea spontaneously resolved once the medication was discontinued. The Patient Introductory Brochure for iPLEDGE, the risk management distribution program mandated by the U.S. Food and Drug Administration for isotretinoin, does not currently include menstrual irregularities as a side effect of treatment; thus, patients who experience this side effect may also experience the unnecessary stress of a possible pregnancy, or, if a minor, explaining a lack of menses to their parent/guardian. This review synthesizes the limited literature available on this subject to advocate for more widespread acknowledgment of menstrual irregularities as a side effect of isotretinoin therapy. To perform the literature review, the search was conducted on June 13, 2020 on PubMed using the following search terms: (((isotretinoin) AND (oligomenorrhea))) OR ((isotretinoin) AND (amenorrhea)) OR ((isotretinoin) AND (PCOS)) OR ((isotretinoin) AND (menstrual irregularities)) OR ((isotretinoin) AND (polycystic ovary syndrome)). All years available were included. Articles were excluded if they were not published in English or did not address the topic of menstrual irregularities in the setting of isotretinoin, with or without the presence of polycystic ovary syndrome. A total of six articles met our criteria and are described.

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Introduction

In 1982, oral isotretinoin was first licensed as a treatment option for severe recalcitrant cystic acne in the United States (McElwee et al., 1991). Since its introduction into the pharmaceu-

tical market, several instances of amenorrhea in women of child-bearing age taking isotretinoin have been reported (Cox, 1988; McElwee et al., 1991; Saljoughi et al., 2017). In each documented instance, the amenorrhea spontaneously resolved once the medication was discontinued. The patient introductory brochure for iPLEDGE, the risk management distribution program mandated by the U.S. Food and Drug Administration for isotretinoin, does not currently include menstrual irregularities as a side effect of treatment; thus, patients who experience this side effect may also

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experience the unnecessary stress of a possible pregnancy, or, if a minor, explaining a lack of menses to their parent/guardian. This review synthesizes the limited literature available on this subject to advocate for more widespread acknowledgment of menstrual irregularities as a side effect of isotretinoin therapy.

Methods

To perform the literature review, a search was conducted on June 13, 2020 on PubMed using the following search terms: (((isotretinoin) AND (oligomenorrhea))) OR ((isotretinoin) AND (amenorrhea)) OR ((isotretinoin) AND (PCOS)) OR ((isotretinoin) AND (menstrual irregularities)) OR ((isotretinoin) AND (polycystic ovary syndrome)). All years available were included. Articles were excluded if they were not published in English or did not address the topic of menstrual irregularities in the setting of isotretinoin, with or without the presence of polycystic ovarian syndrome (PCOS). A total of six articles met our criteria (Fig. 1; Table 1).

Results

There are several case reports that document menstrual abnormalities associated with female patients who are not taking oral contraceptive pills (OCPs) to regulate their menstrual cycles. For instance, a 1988 case report by Cox (1988) described a 14-year-old girl who was 10 weeks into a course of isotretinoin when she reported that she had not menstruated during that time frame despite having regular menstruation for the 3 years prior. Ten days after stopping the medication, her menstruation resumed (Cox, 1988). Furthermore, in a 2016 trial of 50 patients started on isotretinoin for acne vulgaris, Saljoughi et al. (2017) reported that 34% experienced a menstruation-related side effect (oligomenorrhea, amenorrhea, or dysmenorrhea) that corresponded with an increase in serum luteinizing hormone (Saljoughi et al., 2017). Additionally, evidence suggests that such cases of amenorrhea are underreported due to the encouraged use of concurrent OCPs while on isotretinoin (Cox, 1988). In a 1991 retrospective study of 466 male and female patients (53.9% male and 46.1% female) on isotretinoin therapy, McElwee et al. (1991) reported that three patients (two

Table 1
Characteristics of included journal articles.

No. of participants in study	No. with menstrual irregularities	PCOS evaluated?	First author, year
466	2	Not assessed	McElwee et al., 1991
1	1	Not assessed	Cox, 1988
5	5	Not assessed	Christmas, 1988
40	8	Not assessed	Kwon et al., 2007
50	17	Confirmed; 10% had PCOS	Saljoughi et al., 2017
N/A	N/A	Confirmed; best practice guidelines	Goodman et al., 2015

N/A, not applicable; PCOS, polycystic ovarian syndrome.

male, one female) experienced increased liver enzymes and two female patients experienced amenorrhea. Another case study reported in the *Journal of the American Academy of Dermatology* demonstrated that a 17-year-old female patient who previously had menstrual cycles lasting 28 days with 5 days of bleeding experienced prolonged menstrual bleeding after initiating isotretinoin. She was taking an OCP. Her bleeding stopped 2 days after isotretinoin was discontinued, but she had another episode of prolonged bleeding after resuming isotretinoin at a later time (Christmas, 1988).

A retrospective chart review of 40 female patients taking isotretinoin found that 8 patients reported new menstrual irregularities. None of the patients were on OCPs, and they presented with normal levels of follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and prolactin. All eight female patients resumed normal menstrual cycles after discontinuation of the drug. The authors concluded that in younger patients, normal menstrual cycles before and after administration of the drug was suspicious for involvement of isotretinoin in altering the menstrual cycles of the patients (Kwon et al., 2007). Despite the prevalence of amenorrhea in women on isotretinoin that has been demonstrated to stop and start with the use of the medication, it was not listed as a potential side effect of the medication during patient education prior to enrollment in iPLEDGE. Thus, menstrual side effects of the medication continue to cause anxiety and confusion within this population due to a lack of patient education.

The best practice guidelines for PCOS that state “girls with severe acne refractory to treatments including isotretinoin may have a 40% likelihood of developing PCOS” (Goodman et al., 2015). This has led to concern over the differentiation between PCOS and menstrual irregularities secondary to isotretinoin treatment. Although PCOS is clearly a confounding factor in evaluating menstrual irregularities, many of the papers evaluated demonstrated that irregularities began and stopped with isotretinoin treatment, leading authors to the conclusion that the effects may be directly related to isotretinoin (Kwon et al., 2007).

Conclusions

The iPLEDGE program is essential in avoiding major maternal-fetal complications associated with isotretinoin use while pregnant, but menstrual irregularities can cause unnecessary anxiety and stress for women taking isotretinoin who are not on OCPs. These women are simply unaware of or uneducated about this as a potential medication side effect. Despite the screening and reporting of other adverse effects with similar incidence rates, amenorrhea continues to be excluded from the list of potential side effects. As of June 2020, the [Absorica highlights of prescription](#)

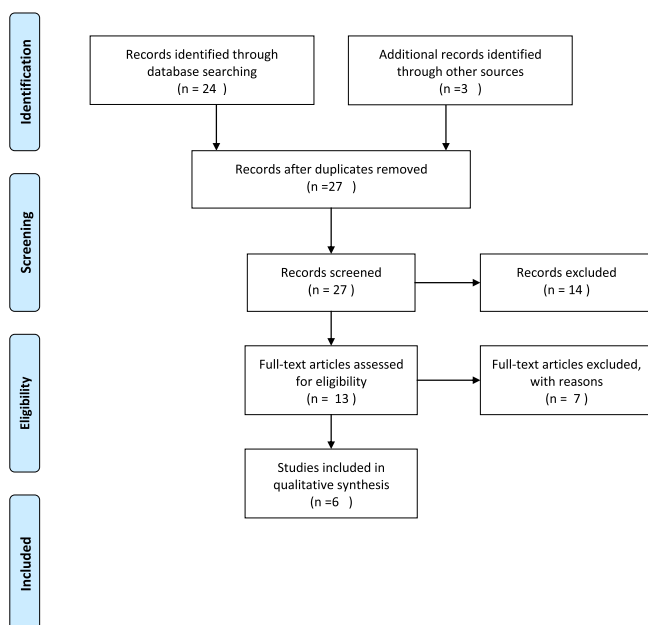


Fig. 1. PRISMA flow diagram.

(updated 2019), Amnesteem package insert (updated 2019), and Myorisan package insert (updated 2018) include abnormal menses, but the iPLEGE booklet does not (iPLEGE, 2016). Thus, we argue that patient care can be improved by including amenorrhea in the list of potential side effects for women of childbearing potential who are planning to take isotretinoin.

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Study Approval

N/A.

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