Gender differences in isotretinoin prescriptions during the COVID-19 pandemic at a U.S. academic medical center

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Abstract
Systemic isotretinoin is a highly effective treatment for severe and refractory acne but carries risk for serious adverse effects such as teratogenicity. The risk mitigation system used in the United States, iPLEDGE, requires all patients on isotretinoin therapy to complete monthly tasks including follow-up visits with their prescriber, and patients with childbearing potential must additionally undergo monthly pregnancy testing. Female patients seeking isotretinoin are disproportionately affected by iPLEDGE-related barriers and have historically been prescribed isotretinoin less than male patients. The onset of the COVID-19 pandemic and updated regulations permitting at-home pregnancy testing and telehealth for monthly follow-up visits presented an opportunity to study the impact of these changes on the isotretinoin gender gap. We performed a single-center analysis to determine whether gender differences in isotretinoin prescription changed at our institution at the beginning of the pandemic. We found that male predominance of isotretinoin prescriptions was greater during the pandemic compared to pre-pandemic (odds ratios: 4.13 vs. 2.86). Furthermore, male patients were more likely to utilize telehealth compared to in-person visits for isotretinoin follow-up relative to female patients (odds ratios: 6.00 vs. 3.62). Despite the newly introduced flexibilities of telehealth and remote pregnancy testing, gender inequity in receiving isotretinoin treatment persists.

Keywords Isotretinoin · Acne · Telehealth · Gender disparities · COVID-19

Introduction
Systemic isotretinoin has been an important treatment for severe acne since its approval in 1982 [8]. Female patients have been reported to be under-prescribed isotretinoin relative to male patients despite being more likely to see a physician for acne [3, 5]. In 2006, the United States Food and Drug Administration (FDA) implemented iPLEDGE, a regulatory system requiring patient registration upon initiation of isotretinoin therapy, which aimed to reduce adverse outcomes and prevent isotretinoin-related teratogenicity. Although iPLEDGE requires all patients to complete monthly counseling and knowledge assessments, patients with childbearing potential must additionally attest to using two forms of contraception, undergo monthly pregnancy testing, and manage a short 7-day prescription pick-up window [4]. These additional requirements may influence the likelihood of prescription of isotretinoin to female patients.

The coronavirus disease 2019 (COVID-19) pandemic catalyzed the adoption of telehealth across specialties including dermatology, not only in the United States but all over the world [1]. In response, guidance on FDA Risk Evaluation and Mitigation Strategy (REMS)-required testing was updated [9], permitting patients on isotretinoin to complete monthly visits via telehealth and undergo pregnancy testing at home instead of at the provider’s office [7]. We hypothesized that these changes could potentially reduce iPLEDGE-related barriers and improve the accessibility of isotretinoin for female patients during the pandemic.

Methods
To evaluate the effect of telehealth and FDA REMS pandemic-related guidance on isotretinoin prescriptions for male and female patients, we analyzed data obtained from...
the University of Chicago’s Clinical Research Data Warehouse. This study was approved by the institutional review board. The criteria for inclusion were dermatology encounters (telehealth visits and in-person visits) during which an adult patient (age > 18 years) was prescribed isotretinoin or topical retinoids. Gender identity was determined from patient-reported demographics extracted from electronic medical records. Fisher’s exact tests with alpha set to 0.05 were used to compare the odds of isotretinoin prescription for male and female patients, with control groups comprised of patients receiving topical retinoids for acne. Topical retinoid prescriptions were selected as the control group as they are commonly prescribed to treat acne in both male and female patients, sometimes in adjunct with other medications, however are rarely prescribed simultaneously with isotretinoin at our institution. Odds ratios during the pandemic period (June 1, 2020 to January 22, 2021) and the pre-pandemic period (June 1, 2019 to January 22, 2020) were further compared. The date range for the pandemic period was selected to capture the time when telehealth visits were conducted concurrently with in-person visits at our institution prior to the widespread availability of COVID-19 vaccination in the United States. Finally, odds ratios were compared between telehealth visits and in-person visits during the pandemic period.

**Results**

In all comparisons, male patients had significantly higher odds of being prescribed isotretinoin than female patients (Table 1). Notably, the gender difference in isotretinoin prescriptions was larger during the pandemic (odds ratio [OR] 4.13; 28% male vs. 9% female; \( P < 0.0005 \)) than before the pandemic (OR 2.86; 33% male vs. 15% female; \( P < 0.0005 \)).

Furthermore, male patients were significantly more likely to be prescribed isotretinoin at both telehealth and in-person visit modalities than female patients (Table 2). The gender difference was larger in the context of telehealth visits (OR 6.00; 41% male vs. 10% female; \( P < 0.0005 \)) compared to in-person visits (OR 3.62; 24% male vs. 8% female; \( P < 0.0005 \)).

**Discussion**

Our results suggest that gender differences in isotretinoin treatment for acne were not reduced during the pandemic despite the approval of telehealth follow-up visits and at-home pregnancy testing. Many factors may influence the relative decreased access to isotretinoin among female patients

### Table 1
Comparison of adult female and male patients receiving isotretinoin relative to topical retinoids for acne during and prior to the COVID-19 pandemic

|                | Topical retinoid | Isotretinoin | OR   | 95% CI Lower | 95% CI Upper | \( P \) value |
|----------------|------------------|--------------|------|--------------|--------------|--------------|
| Pre-pandemic,a |                  |              |      |              |              |              |
| Female         | 496 (85.4)       | 85 (14.6)    | Reference |
| Male           | 151 (67.1)       | 74 (32.9)    | 2.86 | 1.96         | 4.16         | <0.0005      |
| Pandemic,b     |                  |              |      |              |              |              |
| Female         | 661 (91.4)       | 62 (8.6)     | Reference |
| Male           | 165 (72.1)       | 64 (27.9)    | 4.13 | 2.74         | 6.21         | <0.0005      |

Abbreviations: CI confidence interval, OR odds ratio

aPre-pandemic encounters are defined as taking place between June 1, 2019, and January 22, 2020

bPandemic encounters are defined as taking place between June 1, 2020, and January 22, 2021

### Table 2
Comparison of adult female and male patients receiving isotretinoin relative to topical retinoids for acne via telehealth and in-person visits during the COVID-19 pandemic

|                | Topical retinoid | Isotretinoin | OR   | 95% CI Lower | 95% CI Upper | \( P \) value |
|----------------|------------------|--------------|------|--------------|--------------|--------------|
| Pandemic: in-person visit,a |              |              |      |              |              |              |
| Female         | 504 (92.0)       | 44 (8.0)     | Reference |
| Male           | 133 (76.0)       | 42 (24.0)    | 3.62 | 2.21         | 5.90         | <0.0005      |
| Pandemic: telehealth visit,a,b |    |              |      |              |              |              |
| Female         | 157 (89.7)       | 18 (10.3)    | Reference |
| Male           | 32 (59.3)        | 22 (40.7)    | 6.00 | 2.70         | 13.27        | <0.0005      |

Abbreviations: CI confidence interval, OR odds ratio

aPandemic encounters are defined as taking place between June 1, 2020, and January 22, 2021

bAll telehealth visits occurred via synchronous video conferencing
including patient preference. For example, pandemic-related changes may have influenced the choice of acne treatment among female patients more than male patients, especially given the wider range of acne treatments available to female patients. Pandemic-related challenges may disproportionately affect the ability of female patients to adhere to strict iPLEDGE guidelines including the use of two forms of contraception [2] and access to pregnancy tests [6]. Furthermore, provider preference may also explain gender differences in isotretinoin prescription during the pandemic. There may be greater reluctance among providers to prescribe isotretinoin to female patients over telehealth due to concerns about the accuracy of home pregnancy tests [7] or, in the case of initiation of treatment, challenges in completion of the iPLEDGE enrollment process.

Our study is limited by the single-center setting, retrospective data acquisition, and availability of gender identity information using our dataset. Although we were able to detect gender differences in receiving isotretinoin for acne, further investigation is needed to characterize this finding. Specifically, our work finds that female patients had relatively fewer isotretinoin prescriptions compared to male patients but does not describe absolute gender differences in prescriptions for the treatment of acne during the pandemic. Though not included in this study, we plan to examine the data to study whether patients were similarly likely to present for acne before and during the pandemic. Future work should examine patient and provider factors influencing the prescription of isotretinoin to female patients, as well as identify opportunities to improve policies that promote safe isotretinoin use while minimizing gender inequity.

**Author contributions** Both authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization: GD and AMRL. Methodology: GD and AMRL. Formal analysis: GD and AMRL. Writing—original draft: GD. Writing—review and editing: GD and AMRL. Funding acquisition: AMRL. Resources: GD and AMRL. Supervision: AMRL.

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**Declarations**

**Conflict of interest** Authors GD and AR declare no conflicts of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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