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Fetal exposure to isotretinoin in Saudi Arabia: a multicenter real-world data analysis from 2015 to 2020

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Abstract

Background: Despite its high efficacy in treating severe acne, isotretinoin is associated with serious side effects, including teratogenicity. However, the extent of isotretinoin exposure during pregnancy in Saudi Arabia remains unknown.

Objectives: This study aims to quantify the extent of fetal exposure to isotretinoin in Saudi Arabia and to evaluate adherence to risk minimization measures approved by the Saudi Food and Drug Authority.

Design: Retrospective cohort study.

Methods: This multicenter retrospective study included a cohort of 6233 women of childbearing ages (WCBAs) who had received isotretinoin therapy between 2015 and 2020. Exposure to isotretinoin use was ascertained from patients' electronic health records and was defined as any positive pregnancy test (urine or serum) or any diagnosis or procedure related to pregnancy occurring during the risk period. We defined the risk period starting from isotretinoin initiation until up to 30 days after the last prescription. We quantified the overall incidence proportion of fetal exposure to isotretinoin by dividing the number of pregnancy cases during the risk period by the total study sample of WCBAs.

Results: The cohort predominantly included young females (20–29 years), with a mean age of 24 years. Only 5% of the WCBAs used contraceptives, and 10% have a record of pregnancy testing. During the risk period, 34 pregnancies were identified, yielding a cumulative pregnancy incidence of 5.6 per 1000 WCBAs. Pregnancy outcomes for exposed women were about 5% of births had defects, while abortions accounted for 14.3% of pregnancies.

Conclusion: Our investigation shows an alarming incidence of fetal exposure to isotretinoin in Saudi Arabia, substantially surpassing global estimates. These results underscore a critical need for enhanced interventions and robust risk minimization strategies tailored to the distinct challenges faced by the Saudi Arabian population.

Plain language summary

Evaluating isotretinoin use during pregnancy in Saudi Arabia

Why was the study done? Isotretinoin is highly effective for treating severe acne but is known to cause serious birth defects if used during pregnancy. The extent to which pregnant women in Saudi Arabia are exposed to isotretinoin was not known. Understanding this exposure is crucial to improve patient safety and adherence to preventive measures. What did the researchers do? The researchers conducted a retrospective study involving 6,233 women of childbearing age who received isotretinoin between 2015 and 2020. They used electronic health records from multiple

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healthcare institutions to identify cases of isotretinoin exposure during pregnancy. The study assessed the frequency of fetal exposure and evaluated adherence to risk minimization measures approved by the Saudi Food and Drug Authority (SFDA). What did the researchers find? The study found a significant incidence of fetal exposure to isotretinoin, with 5.6 cases per 1,000 women of childbearing age, which is much higher than global estimates. During the study period, 34 pregnancies were identified among isotretinoin users, with a notable percentage resulting in birth defects (5%) and abortions (14.3%). The adherence to contraceptive use (5%) and pregnancy testing (10%) among isotretinoin users was low, indicating a gap in following SFDA guidelines. What do the findings mean? These findings highlight a critical need for improved regulatory strategies and interventions to prevent fetal exposure to isotretinoin in Saudi Arabia. Enhanced measures might include better education on contraceptive use, stricter enforcement of pregnancy testing, and the integration of digital healthcare solutions to ensure adherence to safety protocols. This study sets a foundation for future efforts to improve the safe use of isotretinoin and protect unborn children from its harmful effects.

Keywords: acne, contraceptive, drug safety, fetal exposure, isotretinoin, pregnancy, REMS, risk minimization, Saudi Arabia, teratogenicity

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Introduction

Isotretinoin approved in 1982 as the first-generation retinoid for severe acne treatment, functions by reducing the size of sebaceous glands and inhibiting sebum production.[1] Despite its high efficacy in treating severe acne, isotretinoin is associated with serious side effects, including teratogenicity. Exposure to isotretinoin during pregnancy can lead to malformations in the central nervous system, skull, face, ears, eyes, and cardiovascular system, as well as the thymus and parathyroid glands.[2] Consequently, the risks associated with isotretinoin use outweigh any potential benefits in pregnant women.[3]

Regulatory agencies worldwide have implemented various programs to improve the benefit-risk ratio of isotretinoin by preventing accidental fetal exposure. The Saudi Food and Drug Authority (SFDA) Risk Minimization Program included a consent form to be signed by women of childbearing potential (WCBP) to acknowledge the risks associated with isotretinoin use. WCBP are required to provide a negative pregnancy test before receiving their first prescription and any subsequent refills, as well as 5 weeks post-treatment. Each prescription is limited to a 30-day supply and only dispensed from pharmacies affiliated with hospitals.[4] WCBP are expected to have been counseled by their physicians about proper contraceptive methods prior to, during, and after treatment with isotretinoin. Similar approach is implemented in the United Kingdom and several European countries. In the United States, the Food and Drug Administration (FDA) implemented the iPLEDGE program which has similar requirements in terms of testing and restrictions on the amount to be dispensed; however, it requires active participation from patients, prescribers, and pharmacists to ensure adherence to risk minimization mandated by the FDA.[3]

In Saudi Arabia, the prevalence of acne is estimated to affect more than half of the population,[5–8] contributing to the widespread use of isotretinoin use. However, the extent of fetal exposure to isotretinoin in Saudi Arabia remains unknown. This study aims to quantify the extent of fetal exposure to isotretinoin in Saudi Arabia and evaluate adherence to risk minimization measures approved by SFDA.

Methods

Study design and participants

In this retrospective cohort study, we analyzed 6233 women of childbearing ages (WCBAs) who received isotretinoin therapy between 2015 and 2020. Electronic health records (EHRs) from four healthcare institutions were employed to identify eligible participants and ascertain pertinent data. Data were included from King Saud University Medical City, Kingdom's Hospital, Ministry of National Guard Hospitals, and King Abdullah University Hospital. WCBAs were defined according to the World Health Organization as females aged 15–49.[9] Based on all available data prior to the start of exposure, we excluded WCBAs diagnosed with premature or natural menopause. Additionally, WCBAs who had undergone procedures leading to sterility, such as hysterectomy, bilateral oophorectomy, or total abdominal hysterectomy, were also excluded from the study. We collected data related to the characteristics of WCBAs within a 6-month timeframe prior to the initiation of isotretinoin therapy. This data comprised essential information such as indications for treatment, existing comorbidities, and the use of concurrent medications.

Exposure definition and follow-up

Isotretinoin exposure was defined as the dispensing of any prescription for the medication. We followed isotretinoin users from the first day of dispensing (index date) to 30 days after the discontinuation of therapy. This established the risk period during which WCBAs must avoid pregnancy due to the teratogenic effects of isotretinoin.

Outcome definition

We defined fetal exposure as occurrence of pregnancy during the risk period. We identified pregnancy using various measurements, such as any positive pregnancy test (urine or serum) or any diagnosis or procedure related to pregnancy, as documented within the EHRs.

Adherence to risk minimization measures

To assess adherence to risk minimization measures, we calculated the use of contraceptives and pregnancy tests among the study cohort based on data collected directly from EHRs, reflecting actual usage reported by healthcare providers and patients. This assessment covered the risk period, starting 30 days before isotretinoin initiation and extending 30 days after the therapy ended.

Statistical analysis

Characteristics of the study sample were estimated based on variable type. We expressed categorical variables as counts and percentages while continuous variables were presented as mean ± standard deviation (SD).

We quantified the overall cumulative incidence of fetal exposure to isotretinoin by dividing the number of pregnancy cases during the risk period by the total study sample of WCBAs. Additionally, fetal exposure to isotretinoin was categorized according to timing of exposure as before, during, or after isotretinoin therapy. Each pregnancy case was manually vetted to ensure accuracy and the fate of pregnancy, which was categorized into normal delivery, stillbirth, abortion, or unknown. The incidence proportion of fetal exposure to isotretinoin was stratified by hospital institution.

To quantify the adherence to risk minimization measures, we divided the number of contraceptive uses and pregnancy tests by the total sample, to show an understanding of the cohort's overall compliance. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental Material).[10]

Results

Study population characteristics

A total of 6233 WCBAs who received isotretinoin therapy between 2015 and 2020 were included in the study. Table 1 presents the demographic and clinical characteristics of the study population. The mean age of the participants was 24.25 years (SD: 6.86), with the majority of the WCBAs belonging to the age group of 20–29. Married WCBAs constituted 12% of the sample, while the majority were single. The distribution of body mass index categories revealed that 38% of the participants had a normal Body Mass Index (BMI) and 39% were overweight. Dermatitis (5.5%), vitamin D deficiency (5.1%), hypothyroidism (2.5%), and

Table 1. Study sample.

Variables	*N* (6233)
Age group (%)	
15–19	1624 (26.05)
20–29	3461 (55.5)
30–39	909 (14.5)
⩾40	227 (3.6)
Unknown	12 (0.2)
Weight, kg (mean (SD))	63.5 (15)
Height, m (mean (SD))	1.58 (0.12)
BMI (mean (SD))	25.4 (5.5)
Weight ranges (%)	
Normal	2363 (38)
Obese	371 (5.9)
Overweight	2426 (38.9)
Underweight	278 (4.4)
Unknown	795 (12.7)
Marital status (%)	
Married	805 (12.9)
Single	4524 (72.5)
Unknown	904 (14.6)
Comorbidities	
Anxiety	71 (1.1)
Asthma	140 (2.2)
Depression	36 (0.5)
Dermatitis	359 (5.7)
Hypertension	48 (0.8)
Hypothyroidism	238 (3.8)
Irritable bowel syndrome	101 (1.6)
Obesity	93 (1.4)
Polycystic ovary syndrome	512 (8.2)
Vitamin D deficiency	819 (13.1)
Acne medications	
Adapalene	450 (7.2)
Clindamycin	643 (10.3)
Dexamethasone	66 (1.05)
Doxycycline	211 (3.4)
Erythromycin	19 (0.3)
Hydroquinone	128 (2.05)
Miconazole	87 (1.3)
Tretinoin	257 (4.1)

polycystic ovary syndrome (2.2%) were the top medical diagnoses identified among the study sample. Previous acne treatments included antibiotics (e.g., clindamycin) and topical retinoids; however, the majority had not been treated with any acne treatment before isotretinoin initiation.

Pregnancy outcomes

During the risk period, a total of 34 pregnancies were identified among the WCBAs, resulting in a pregnancy incidence proportion of 5.6 per 1000 WCBAs (Figure 1). Only one WCBA was pregnant at the time of isotretinoin dispensing (0.2 per 1000 WCBAs), while the majority of cases occurred during isotretinoin exposure (4.6 per 1000 WCBAs). The outcome of the majority of pregnancies (62%) was unknown with respect to delivery. Normal deliveries accounted for 5% of the cases, while 5% of deliveries were with defects, and 14.3% of pregnancies ended in abortion (Figure 2).

Adherence to risk minimization measures

The adherence to contraceptive use and pregnancy testing is presented in Figures 3 and 4. Overall, 5% of the WCBAs used contraceptives, with 60% using oral contraceptives and 4% using intrauterine devices. Pregnancy tests were performed for 10% of the participants. The adherence proportion varied among different age groups and marital statuses.

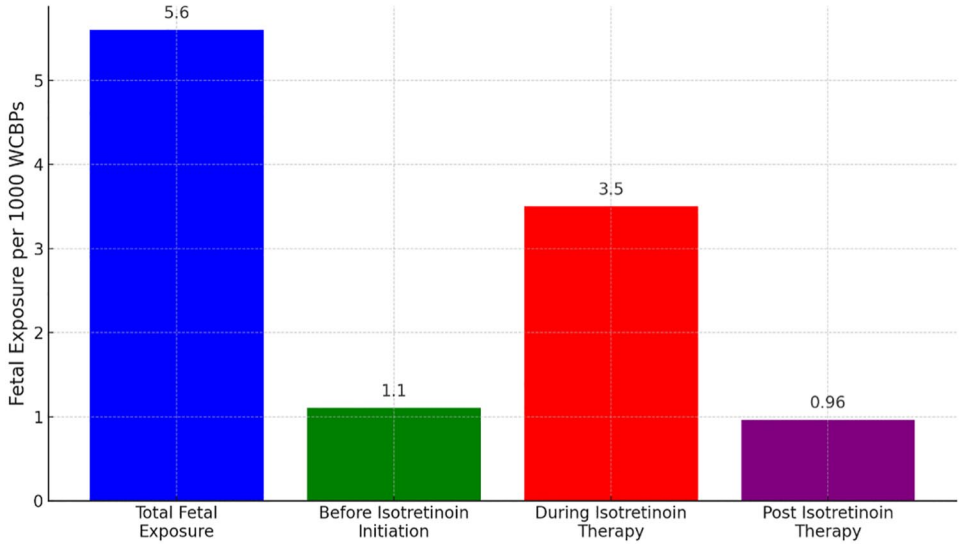

Figure 1. Incidence proportion of fetal exposure to isotretinoin per 1000 WCBPs.

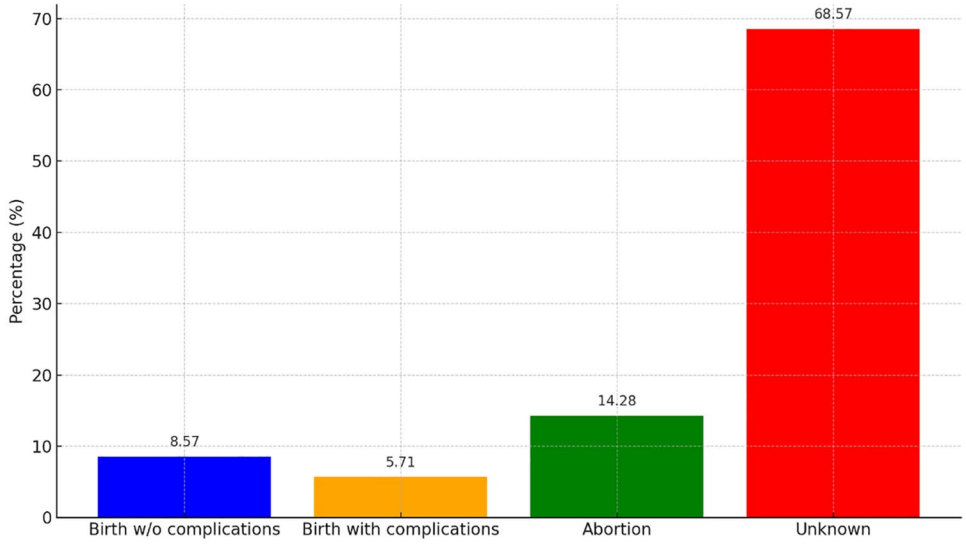

Figure 2. Pregnancy outcome distribution.

Discussion

Our research represents the first study to document the incidence proportion of fetal exposure to isotretinoin in Saudi Arabia using real-world data. The observed incidence of pregnant women exposed to isotretinoin in Saudi Arabia is alarmingly higher in comparison to incidence reported globally. Research conducted on the iPLEDGE program in the United States has demonstrated that 2 out of 1000 pregnant women experienced exposure to isotretinoin.[11,12] Moreover, literature from Canada and Estonia reveals a higher incidence, with 3 out of 1000 pregnant women exposed to isotretinoin.[13,14] A systematic review of studies across Europe has reported a lower rate of 1 out of 1000 pregnant women exposed to isotretinoin.[15,16] Our findings indicate that approximately 6 out of 1000 pregnant women

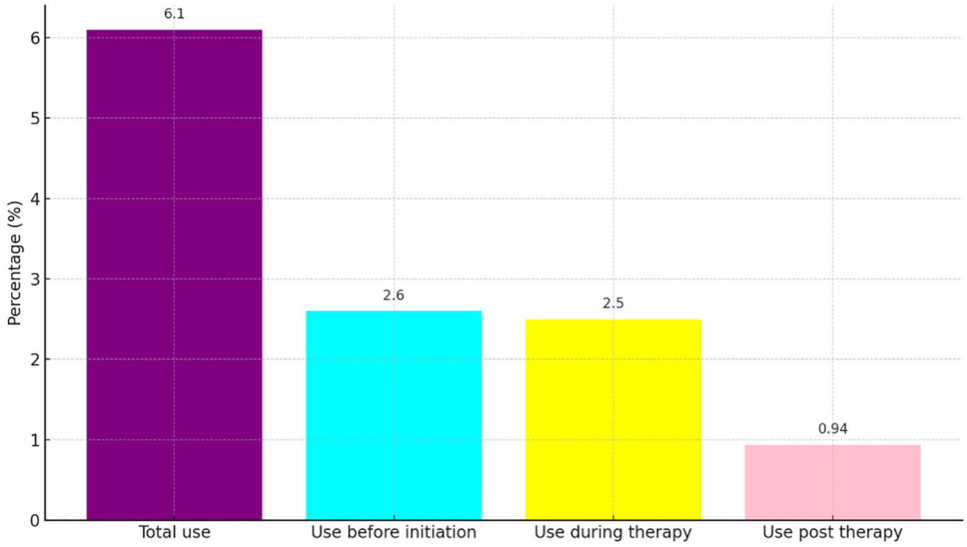

Figure 3. Study sample adherence to contraceptive use.

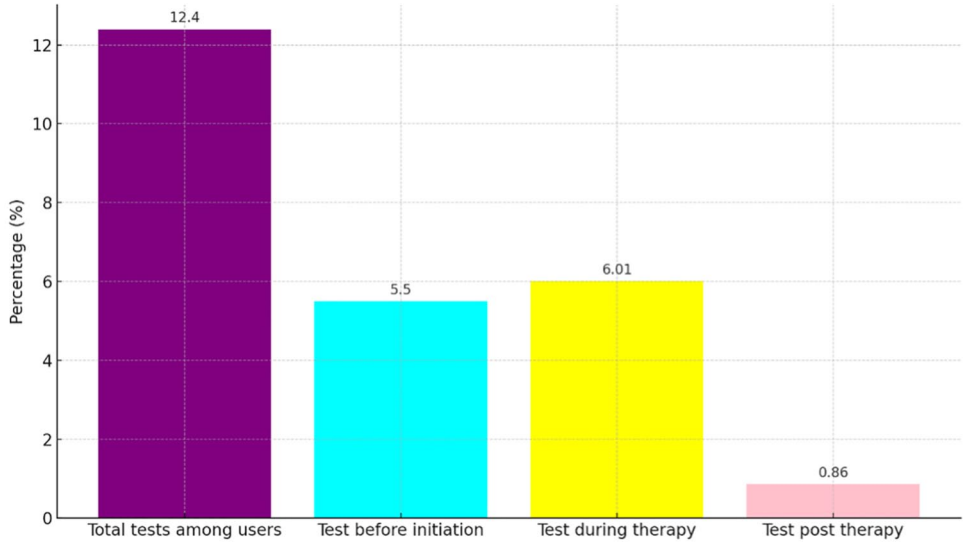

Figure 4. Study sample adherence to pregnancy test.

were exposed to isotretinoin, a figure that is double the highest documented rate worldwide. Although abortion is permitted if the fetus is less than 4 months old, only 14% of pregnancies exposed to isotretinoin ended in abortion.

It is crucial to consider that the studies conducted in the Western countries specifically focused on WCBAs who were at risk of becoming pregnant, in accordance with their respective legal frameworks. In contrast, our analysis incorporated WCBAs from Saudi Arabia, regardless of their risk of becoming pregnant. In Saudi Arabian cultural and legal norms, pregnancy outside of legal marriage is not permitted.[17] As only 12% of WCBA in our study are married, the denominator includes a significant number of WCBAs for whom pregnancy is rare. This may potentially lead to an underestimation of the actual incidence proportion. This observation underscores the need for

heightened awareness and intervention in the region, as even a conservative estimate demonstrates a markedly elevated incidence of fetal exposure to isotretinoin compared to other countries. This highlights the importance of understanding the challenges of currently approved risk minimization strategies to develop more effective strategies tailored to the specific needs of the Saudi Arabian population.

One of the key risk minimization strategies to reduce fetal exposure to isotretinoin is the appropriate use of contraceptives.[18] Ensuring effective contraceptive use is vital in preventing unintended pregnancies among women who are prescribed isotretinoin. However, contraceptive use and access vary significantly across different regions worldwide, influenced by factors such as cultural, social, and economic circumstances. According to the World Health Organization, as of 2019, approximately 65% of women aged 15–49 years who were married or in a union were using some form of contraception.[19] Regionally, contraceptive use ranged from 49.5% in Northern Africa[20] to 68% in North America.[21] In comparison, Saudi Arabia reported a contraceptive prevalence rate of around 30%[22,23] among married women in the same age group, which is notably lower than the global average. In our study sample, there were 805 WCBPs identified as married. Under the assumption that all contraceptive prescriptions were distributed to these married WCBPs, the resulting percentage approximates ~30%. The comparatively lower rate of contraceptive use in Saudi Arabia highlights the need for targeted interventions that address barriers to access and uptake, such as cultural sensitivities, basic insurance policy coverage,[24] and a lack of awareness about different contraceptive methods. Majority of isotretinoin users (56.8%) reported that they were not advised by their healthcare providers to use two contraceptive methods before starting the medication.[25] Moreover, a study conducted in Saudi Arabia found that pharmacists working in community pharmacies demonstrate inadequate awareness concerning the risk prevention associated with isotretinoin, with only 11% recommending the utilization of two contraceptive methods.[26] Healthcare professionals in Saudi Arabia must be equipped with culturally appropriate resources and training to effectively counsel patients on contraceptive use, particularly for those prescribed isotretinoin.

Another important risk mitigation measure is pregnancy test before starting isotretinoin. In a study conducted in Saudi Arabia, only 50% of physicians requested pregnancy tests for female patients prior to isotretinoin treatment, with 79% never tested for pregnancy during isotretinoin treatment.[27] Moreover, in a survey of married Saudi females, only 66% were informed to perform pregnancy tests before initiating isotretinoin.[25] In our study sample, there were 805 WCBPs identified as married. Assuming that the pregnancy tests were conducted by these married WCBPs, the resulting percentage is approximately 40%. Inadequate adherence to pregnancy tests was also observed in other countries including Canada in which 44%–67% reported having pregnancy tests.[18] Future research should explore both the patient-related and diverse contextual elements that may influence the effectiveness of risk mitigation strategies, aiming to tailor the strategy to align with the Saudi cultural context and improve the burden-to-benefit ratio.

The findings from our study align with recent literature on isotretinoin and pregnancy in Saudi Arabia[25,27] underscoring a pressing need for regulatory enhancements and collaboration among key stakeholders. Despite the global adoption of risk minimization measures for isotretinoin—including stringent programs like iPLEDGE—evidence suggests limited success in curbing fetal exposure.[11,12] In the United States, a thorough review by the Inspector General Office revealed that the efficacy of most Risk Evaluation and Mitigation Systems (REMS) remains uncertain, largely due to incomplete data submissions from sponsors to the FDA.[28] Relying solely on sponsors for pertinent risk assessment data may not be the optimal approach for effective risk minimization plan implementation. In today's age of digital health, big data, real-time analytics, and artificial intelligence, it is imperative that risk minimization evaluations transition from passive to active systems and become more comprehensive in scope.

Digital solutions present a powerful means to bolster compliance with risk minimization protocols. By utilizing unified healthcare records, medical professionals can instantly access comprehensive patient histories, such as pregnancy test outcomes and contraceptive usage. This centralized digital framework streamlines patient data verification.

Moreover, integrated digital systems enable the incorporation of hard-stops in both prescribing and dispensing drugs, especially pertinent to WCBP who don't adhere to the Risk Minimization Programs. One healthcare center adopted robust informatics solutions that encompassed specific medication restrictions, altered ordering processes, and mandatory pharmacist checks. Developed with insights from specialized providers and pharmacists, these measures ensured adherence to the REMS program, especially for pulmonary arterial hypertension medications. Notably, after the informatics implementation, the percentage of pregnancy tests carried out within 30 days of medication order surged from 36.4% to 100%.[29] These digital solutions address the issues of non-adherence to protocols by physicians and pharmacists, ensuring that all healthcare professionals consistently follow established safety measures.

Limitations

Our research marks the first attempt within the regional and local context to estimate fetal exposure to isotretinoin using real-world data. By incorporating a diverse range of hospitals—including academic, private, and governmental institutions—we enhance the generalizability of our findings. Furthermore, each pregnancy case was manually reviewed to ensure rigorous validation and data confirmation. However, it's important to recognize the study's limitations when interpreting the results. Our study included all WCBP prescribed isotretinoin and did not explicitly exclude those using additional teratogenic medications. As a result, some participants may have adhered to risk minimization measures for other medications, potentially leading to better overall adherence than we could directly assess in this study. Limited data from other countries in the region hampers a comprehensive discussion of risk minimization strategies. This underscores the need for further research to evaluate and improve adherence to isotretinoin risk minimization protocols across different regional settings. Addressing this gap would help in identifying best practices and enhancing patient safety. Furthermore, our research may not fully capture all WCBPs in Saudi Arabia on isotretinoin, given that data was sourced only from Riyadh hospitals. Potential misclassification of marital status could lead to underestimation of our findings. Additionally, actions such as contraceptive use and pregnancy tests conducted outside the included hospitals aren't captured, increasing the likelihood of underestimating the results.

Conclusion

Our investigation shows an alarming incidence of fetal exposure to isotretinoin in Saudi Arabia, substantially surpassing global estimates. These results underscore a critical need for enhanced interventions and robust risk minimization strategies tailored to the distinct challenges faced by the Saudi Arabian population. As the digital era progresses, leveraging technological solutions such as unified healthcare records and advanced informatics can significantly enhance compliance with risk minimization protocols. Our study sets a baseline to examine the effectiveness of future updates of precautionary measures concerning isotretinoin use.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of each participating institution including King Saud University Medical City (E-21-6119), the King Abdullah International Medical Research Center (NRC22R/166/04), Saudi Food and Drug Authority (2021_12), and King Abdullah bin Abdulaziz University Hospital (22-0040). Due to the retrospective nature of the study and the use of de-identified data, the requirement for informed consent was waived. We ensured that the study was conducted in strict accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Author contributions

Yasser Albogami: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Supervision; Visualization; Writing – original draft.

Ohoud Almadani: Data curation; Formal analysis; Investigation; Visualization; Writing – review & editing.

Sumaya N. Almohareb: Investigation; Project administration; Resources; Validation; Writing – review & editing.

Sultan Alshehri: Data curation; Investigation; Methodology; Project administration; Writing – review & editing.

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Mona Anzan: Investigation; Validation; Writing – review & editing.

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Abdulaziz Alhossan: Resources; Supervision; Writing – review & editing.

Adel Alrwisan: Conceptualization; Methodology; Resources; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Disclosure

The views expressed in this paper are those of the author(s) and do not necessarily reflect those of the SFDA or its stakeholders. Guaranteeing the accuracy and the validity of the data is the sole responsibility of the research team.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. Data will be shared in compliance with applicable privacy laws, ethics regulations, and institutional guidelines.

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Supplemental material

Supplemental material for this article is available online.

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