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Pores and Cons: Isotretinoin's Efficacy, Side Effects, and Gender Biases

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By

Hanna Heaton Wellenstein
[redacted]

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School: Miss Hall's School
Grade: 12
Teacher: Donna Daigle

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Accutane, more scientifically known as isotretinoin, is a retinoid medication commonly used to treat severe acne. It has improved many patients' lives but also raises significant questions about its safety and side effects. Retinoids like Accutane are derived from vitamin A, an essential nutrient that has a large role in bone and skin development. A deficiency in vitamin A has been proven to cause many skin diseases, including acne and rosacea, while an excess does not lead to any further health issues if it occurs naturally within the body. Conversely, too much synthetic vitamin A has been linked to several side effects. The list of possible complications associated with isotretinoin is expansive and includes, but is not limited to: dry, itchy skin; nosebleeds; joint and muscle pain; hair thinning; and depression or suicidal thoughts (Knutel, 2022). There is also a significant risk of birth defects for children born to patients on Accutane. This phenomenon, called Accutane embryopathy or fetal retinoid syndrome, is a serious and carefully monitored concern. Patients who can become pregnant are subjected to regimented protocols while on the medication, complicating the entire treatment process. As a scientist, I'm fascinated by the inner workings of this drug, especially the connections and comparisons between its positive impact and associated dangers. As a former patient, I care deeply about the ethical considerations surrounding isotretinoin, specifically the unnecessary pressure it puts on biologically female patients to adhere to restrictive legislation regarding reproduction.

Oral isotretinoin was first approved by the FDA to treat severe acne in 1982, and it remains the only acne medication that impacts all factors of acne production. To fully

comprehend the long-term impact of isotretinoin, it's important to understand how the drug works at the molecular level. Accutane works to clear and permanently prevent the accumulation of acne by influencing cell cycle progression, cellular differentiation, and cell apoptosis (Layton, 2009). But how exactly does isotretinoin manage to do all of these things? It works as a pro-drug. In other words, when isotretinoin enters the body, it is transformed into a series of metabolites. The five most common metabolites of isotretinoin are 13-*cis*-4-*oxo*-retinoic acid (4-*oxo*-isotretinoin), all-*trans*-RA (tretinoin), all-*trans*-4-*oxo*-retinoic acid (4-*oxo*-tretinoin), 9-*cis*retinoic acid, and 9-*cis*-4-*oxo*-retinoic acid (Layton, 2009). These metabolites can bind to and activate receptors, which are proteins that receive signals and cause cells to change their function. While each metabolite has a different role, the most important are tretinoin and 4-*oxo*-tretinoin, which bind to the retinoic acid receptors (also known as RARs, nuclear receptors that are activated by ligands) to inhibit cell growth. (Zoubloulis, 2006). Within each isotretinoin patient, there are different plasma concentrations of the five metabolites listed above. This explains why some patients have very different reactions to the drug, and why the possible side effects have so much variation (Layton, 2009).

Isotretinoin itself has some remarkable intrinsic qualities as well. It acts in a receptor-independent manner, and, through direct protein interactions, can influence cell signaling pathways. This induces apoptosis in sebocytes, shrinking the sebaceous glands and leading to reduced sebum production (Layton, 2009). Isotretinoin also decreases hyperkeratinization, which is an increased thickness of the outer layer of skin caused by an excess of keratin. Finally, isotretinoin exerts anti-inflammatory activity by inhibiting the migration of polymorphonuclear leukocytes (a type of immune cell) (Price, 2007) and monocytes (a type of white blood cell)

(Martinet, 1994) into the skin and bloodstream. Together, these molecular systems work to significantly reduce sebum production, lower surface acne, and reduce inflammation, leading patients to long-term clear skin.

While isotretinoin and its associated metabolites work together to achieve many positive results in patients, the risk of side effects is severe, and, as a former patient, quite terrifying. Dermatologists and researchers are still unsure of the full extent of possible complications, but some of the most common reactions include sensitivity to sunlight; dry mouth, skin, and eyes; nosebleeds; bowel inflammation; decreased night vision; and serious birth defects in children of patients (Ross-Flanigan, 2020). The first case of Accutane embryopathy was recorded in 1983, only one year after the drug was first approved by the FDA. In 1985, a man named Dr. Edward Lammer decided to study these cases, reviewing a total of 154 pregnancies of Accutane patients that had been reported to either the FDA or the CDC (Knutel, 2022). Of these 154 pregnancies, there were 95 elective terminations and 59 continued pregnancies. Of those 59, 12 ended in miscarriage, 6 were stillborn with obvious health issues, 18 were live-born with obvious health issues, and the final 26 were born without complications. In each of these cases, the patients had been using the drug during the first trimester of their pregnancy, or for even longer. These early months are a critical and sensitive time for an embryo, where the major organs begin to develop. Vitamin A derivatives, known as retinoids, are directly involved in the expression of *Hox* genes, which have a big role in the formation of an embryo around the fourth week of development. Synthetic vitamin A that enters an embryo's system during this stage is likely to cause damage to the internal organs during their formation because higher amounts of retinoids cause the *Hox* genes to malfunction, disrupting the genetic control of the embryo's body shape

(Tantibanchachai, 2014). Dr. Lammer also provided dermatologists with a comprehensive list of the specific abnormalities children may develop from parents on Accutane, including an underdevelopment of facial bones, structural defects of the heart, hydrocephalus, mild to moderate intellectual disabilities, and cleft palates. This study concluded and demonstrated the severity of Accutane embryopathy and prompted dermatologists and scientists to be more cautious with their treatment and patient monitoring guidelines (Knutel, 2022).

To regulate isotretinoin usage and ensure patients understand the risks of pregnancy, a company called Roche Laboratories created the Accutane Pregnancy Prevention Program (PPP) in mid-1989. At its inception, this program was primarily an educational resource for patients, which included a list of concepts that doctors were meant to fully explain to their patients before prescription, in addition to consent forms and brochures offering patient referrals so they could obtain proper birth control methods (Knutel, 2022). Roche implemented a tracking study to confirm that doctors and patients were using the kit as they intended. Unfortunately, they found that many dermatologists were not referring to the kit when explaining the risks of isotretinoin, and many patients were conceiving despite the warnings. Following this failed study, the drug was briefly discontinued in 2009. In 2012, when the drug had been returned to the market, lawsuits were brought against Roche Pharmaceuticals by former Accutane users, stating that the drug gave them bowel disease and that they weren't properly informed of this possibility when they first decided to go on the medication (Knutel, 2022). Roche Pharmaceuticals lost these lawsuits and because of this, researchers and pharmaceutical companies knew that they needed to improve their preventative measures, both to protect their patients' health and protect themselves legally and financially

When I had my first pre-Accutane appointment 18 months ago, I was shocked at the strict guidelines I had to follow, even months before I began taking the medication. To begin, I had to sign a consent form, entitled *Patient Enrollment Form for Patients Who Can Get Pregnant.* (iPLEDGE REMS, n.d.) This form was found on a website known as iPLEDGE, a tracking system required by the FDA in 2005, made to monitor Accutane patients. By signing this form, I agreed that if I were to become pregnant, I would have to report information about my pregnancy not only to my doctor but also to the makers of isotretinoin and government health regulatory authorities (iPLEDGE REMS, n.d.). Going into treatment, I was already aware that I would be required to take monthly pregnancy tests. However, I did not know that the iPLEDGE REMS reporting system did not trust me to do these independently. Not only was I required to take two tests before starting the medication and one per month after, but I had to do each test at an approved lab. Once a month, with no approved lab near my house, I traveled over an hour each way to take a five-minute test and go home. In addition to being an inconvenience for many patients, the IPLEDGE program hinders their privacy, by requiring them to submit a monthly report of the forms of contraceptives they use. These reports are intrusive, and in my experience as a patient, very uncomfortable to fill out.

The Accutane process forces women who are interested in treatment to undergo far harsher regulations than biologically male patients. As of now, there have been no patterns of birth defects in studies of babies whose fathers were taking isotretinoin at the time of conception, but there are also not enough studies to determine that there is no effect on sperm, so there is still a possible risk. Rather than educate biologically male patients, the iPLEDGE REMS handbook

frames this as another responsibility for biologically female patients. They're told that if they are worried about getting pregnant by a partner on Accutane, they should simply use protection, putting the burden completely on women, and not on male Accutane patients. With patients who can't get pregnant, there isn't the same level of fear and precaution, even though the effects are still unclear.

As the only acne medication that can yield such powerful results, it's unfortunate that not only are the possible side effects of isotretinoin dangerous and severe, but the process of obtaining the medication is inconvenient, intrusive, and for some, impossible, due to the strict regulations. Isotretinoin manufacturers and associated companies place undue pressure on women to monitor themselves in a way that other patients are not required nor expected to do. This inequity regarding the burdensome expectations on female patients is not at all new to the medical field, and hopefully, soon, there will be a way to ensure patient safety on this medication without hindering their privacy or way of life.

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