Journal of Assisted Reproduction and Genetics (2025) 42:2793–2799
https://doi.org/10.1007/s10815-025-03567-6

REPRODUCTIVE PHYSIOLOGY AND DISEASE

Treatment with isotretinoin can improve de novo sperm production in nonobstructive azoospermia or cryptozoospermia

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Received: 25 March 2025 / Accepted: 17 June 2025 / Published online: 19 July 2025

Abstract

Purpose Retinoic acid (RA), a metabolite of vitamin A, is required for mammalian spermatogenesis. Clinically, intratesticular RA concentrations are lower in infertile men. In pilot studies, RA treatment is associated with increased ejaculated sperm counts in men with oligospermia and with de novo ejaculated sperm in nonobstructive azoospermia (NOA). We evaluated whether oral isotretinoin could improve sperm production in men with NOA and cryptozoospermia.

Methods Single-center, prospective, repeated measures analysis of infertile men with NOA or cryptozoospermia who received isotretinoin (20 mg twice daily) and had metabolic and semen evaluations over 3–9 months. All etiologies of infertility were included, as were subjects with prior sperm retrieval procedures. The primary endpoint was attaining reliable motile ejaculated sperm for IVF-ICSI.

Results Among $n = 30$ consecutive men undergoing isotretinoin treatment, 26 (87%) were azoospermic and 4 (13%) were intermittently cryptozoospermic. Among azoospermic men, 24 (92%) had prior testicular procedures and 6 (23%) had a history of cryptozoospermia. Overall, 11/30 (37%) of patients developed reliable, motile ejaculated sperm counts with treatment. When evaluating biopsy histology, those with maturation arrest patterns had the highest response (6/11 or 54%) to therapy. Side effects included 30 (100%) men with dry skin/chapped lips, 4 (13%) rashes, 14 (47%) irritability, and 5 (17%) with altered cholesterol panels.

Conclusion Intratesticular retinoic acid deficiency may underlie some forms of severe male factor infertility. Treatment with isotretinoin increases sperm production in some men with NOA or cryptozoospermia to the point of obviating the need for testicular sperm retrieval procedures.

Keywords Retinoic acid · Azoospermia · Male infertility · Spermatogenesis · IVF-ICSI

Introduction

Azoospermia, the complete absence of sperm in the ejaculate, affects approximately 1% of all men and 15% of infertile men [1]. It is classified as either obstructive or nonobstructive in nature. Obstructive azoospermia is amenable to treatment with microsurgical reconstruction or sperm retrieval and assisted reproductive technology [2]. However, nonobstructive azoospermia (NOA) is more challenging to treat as it is associated with severely impaired spermatogenesis and the variable presence and heterotopic location of testicular sperm [3]. With the exception of gonadotropin treatment in gonadotropin deficient men [4], there are no FDA-approved medical treatments for male infertility due to azoospermia. The current standard of care in these cases employ invasive testicular surgical sperm extraction procedures coupled with in vitro fertilization by intracytoplasmic sperm injection (IVF-ICSI) [5]. Unfortunately, these procedures fail to yield sperm in 50% of cases [5]. Therefore, new and novel approaches to the treatment of infertility due to azoospermia are needed.

For 100 years, it has been recognized that retinoic acid (RA), a metabolite of vitamin A, is crucial for normal

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spermatogenesis [6]. RA is intimately involved in the regulation of gene expression during differentiation of spermatogonia and spermatids, proper germ cell adhesion to Sertoli cells, and spermiation [7]. In addition, intratesticular RA levels have been shown to correlate with sperm output in infertile men, a finding that brings its relevance directly into the clinical arena [8, 9].

Subsequent pilot studies involving RA supplementation in infertile men, specifically with isotretinoin (13-cis retinoic acid), have confirmed its clinical importance. Isotretinoin supplementation given to 20 men with infertility due to oligoasthenoteratozoospermia led to significant improvements in ejaculated sperm counts in half of those treated and included several spontaneous pregnancies [10]. A subsequent study tested whether infertile men with azoospermia might also benefit from treatment with isotretinoin [11]. Following 6 months of treatment, sperm were observed in the centrifuged pellets of 4 of 9 men after at least 3 pelleted baseline semen samples were negative for sperm. Moreover, a fifth patient had a positive repeat sperm surgical sperm retrieval procedure ultimately resulting in a live birth after a previously having had a negative sperm retrieval procedure. These early studies are provocative in that they support our understanding of the biology of spermatogenesis and suggest that RA supplementation might be a novel way for currently untreatable men with nonobstructive azoospermia to have biological children.

Continuing this line of reasoning, we sought to extend the findings of this earlier work. Our aim was to investigate the efficacy of oral isotretinoin to improve sperm production in men with nonobstructive azoospermia and intermittent or unreliable cryptozoospermia. The primary endpoint was to ascertain whether isotretinoin therapy could induce sufficient reliable, ejaculated motile sperm for IVF-ICSI and thereby avoid surgical sperm retrieval procedures.

Materials and methods

We conducted a retrospective analysis on a single-center, single cohort, observational study of repeated measures design. Institutional Review Board review was obtained for the study (WCG IRB, Princeton, NJ; #1–1,818,243-1).

Study subjects

Consecutive infertile men were offered isotretinoin therapy from December 2022 until December 2024. Inclusion criteria were those with nonobstructive azoospermia confirmed by at least 2 centrifuged pellet analyses, or nonobstructive cryptozoospermia in which ejaculated sperm was either present in the past but not present on current evaluation, or those in whom centrifuged pellets revealed the intermittent presence of ejaculated sperm that was insufficient for IVF-ICSI. Patients with adequate ejaculated sperm to proceed to IVF-ICSI were not offered isotretinoin therapy. Study subjects included all etiologies of infertility, whether genetic or acquired in nature, and whether definable or not. Patients who had undergone any diagnostic (e.g. testis FNA Mapping or testis biopsy) or therapeutic (e.g., testicular sperm aspiration, conventional extraction or microdissection extraction) sperm retrieval procedures, and that were either successful or not in yielding sperm, were offered therapy. Additionally, those individuals having had prior, but not current, treatment with clomiphene citrate, anastrozole, human chorionic gonadotropin or follicle stimulating hormone were included in the study. Lastly, subjects currently taking these therapies for at least 3 months without a positive semen response were also offered isotretinoin therapy.

Intervention and outcomes

Subjects received isotretinoin at a dose of 20 mg twice daily (Fig. 1). A 0.5 mg/kg dosing regimen was chosen based upon FDA guidance. Treatment duration was a minimum of 6 months or until reliable ejaculated sperm developed. Based upon iPLEDGE®-REMS requirements for patient monitoring and prescription renewal [12], monthly patient assessments were performed along with periodic clinical assessments that included metabolic and semen evaluations (Fig. 1). A basic metabolic profile, cholesterol panel, complete blood count, and serum testosterone, follicle stimulating hormone (FSH) and luteinizing hormones (LH) levels were obtained at baseline prior to starting isotretinoin and then repeated after 4 weeks of initiating therapy. Semen evaluation with centrifuged pellet analyses were conducted as per WHO protocol [13] at baseline and 3-month intervals while medication was given.

The primary outcome of the study was the evaluation of the effectiveness of isotretinoin to generate sufficient (greater than 1 morphologically normal sperm per egg at ICSI), reliable (sperm present in at least 2 consecutive semen samples), motile, ejaculated sperm to allow patients to proceed to IVF-ICSI without the need for testicular sperm retrieval procedures. This was termed a "complete response" to therapy. A secondary outcome assessed the ability of testicular sperm retrieval procedures to yield sufficient sperm when sperm was not found in the ejaculate after isotretinoin therapy, which was termed a "partial response."

Statistical analysis

Clinical characteristics, side effects and complications among study subjects were presented descriptively. Baseline and on-treatment laboratory values were compared using paired *t*-tests without correction for multiple comparisons.

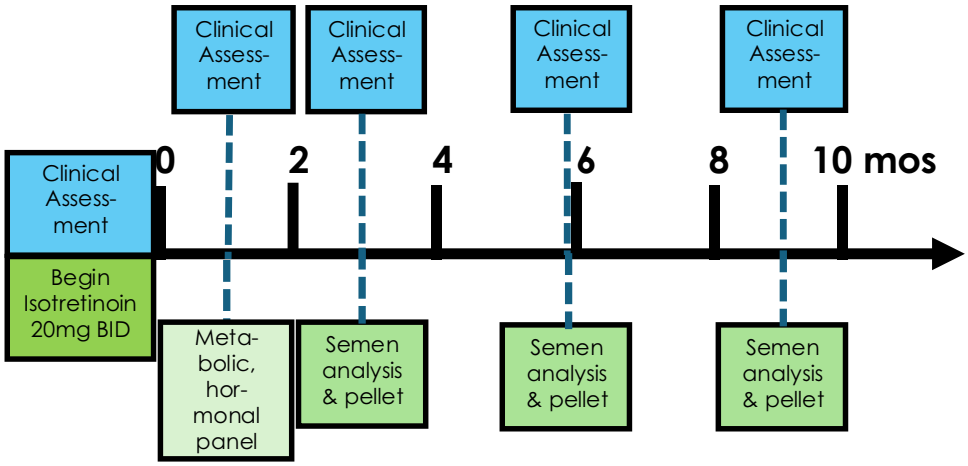

Fig. 1 Isotretinoin study design, timeline and interventions. Regular clinical and semen assessments were conducted throughout the study period. Note: mos = months; BID = twice daily

The proportion of men responding to therapy with sperm in their ejaculates by infertility category (Table 3) and testicular histology (Table 4) were compared using an extended Fisher's exact test without corrections for multiple comparisons. Calculations were performed using STATA version 10 (College Park, TX). For all comparisons a *p*-value of less than 0.05 was considered significant.

Results

Subject demographics

Among the 31 men enrolled, 30 completed the course of treatment. One subject dropped out of the study due to side effects and is not included in the analysis. The mean age of study subjects was 37.9 years (±4.7 years) and mean testicular volumes were 14.4 mL (±4.8 mL) and 13.8 mL (±3.9 mL), on the right and left sides, respectively. The laboratory evaluation of study subjects at baseline and after 4 weeks on treatment are outlined in Table 1. Laboratory assessment demonstrated only a significant increase in serum triglycerides ($p = 0.04$) with isotretinoin treatment; however, no subject had an elevation of serum triglycerides to above 500 mg/dl and no subject experienced pancreatitis. A mild significant increase in serum AST was also noted but was not clinically significant.

Among those completing treatment, 26 (87%) were azoospermic, and 4 (13%) were cryptozoospermic. Six men with azoospermia (20%) had a past history of cryptozoospermia. Among men with azoospermia or cryptozoospermia respectively, 24/26 (92%) and 3/4 (75%) had previously undergone testicular sperm retrieval or fine needle aspiration (FNA) mapping [14] procedures (Table 2). Regarding the etiology of infertility, 23/30 had idiopathic infertility; 3/30 had unilateral or bilateral undescended testes; 3/30 harbored a genetic diagnosis [46, XY,t(2;7;8)(q34;q31.2;q22.1); 46, XY,t(15:16)(q11.2;p13.1), and 46, XY 16qh+] and 1/30 had a history of crushed pelvis.

Table 1 Baseline and on-treatment laboratory values for subjects receiving isotretinoin

Measure (units)	Baseline	On-treatment	*p*-value vs. baseline
Testosterone (ng/dl)	444 ± 147	463 ± 155	0.34
FSH (IU/L)	17.5 ± 11.9	18.6 ± 10.9	0.37
Hemoglobin (g/L)	14.9 ± 1.1	14.9 ± 1.3	0.56
Cholesterol (mg/dl)	197 ± 49	204 ± 39	0.47
HDL (mg/dl)	52 ± 18	49 ± 18	0.06
LDL (mg/dl)	127 ± 47	130 ± 33	0.83
Triglycerides (mg/dl)	115 ± 72	129 ± 79	**0.04**
AST (U/L)	23 ± 8.7	28 ± 13	0.03
ALT (U/L)	29 ± 14	33 ± 13	0.22
Creatinine (mg/dl)	0.95 ± 0.16	0.96 ± 0.18	0.62

Notes: All values are means ± standard deviations

Study outcomes

Among 30 treated subjects, 11 (37%) developed reliable, motile ejaculated sperm counts with isotretinoin treatment. Among azoospermic men, 7/26 (27%) responded. Among cryptozoospermic men, 4/4 (100%) responded (Table 3). Mean total motile sperm count (TMC) achieved among all responders was 48,000 sperm. The TMC response by individual in the eleven men who developed sperm in their ejaculates is illustrated in Fig. 2. There was no clear association between the magnitude of the TMC response and the cohort status (i.e., azoospermia or cryptozoospermia; prior TESE with or without sperm found). Median ejaculated TMCs in the two categories of subjects is outlined in Table 3. Response times to achieve motile ejaculated sperm counts are illustrated in Fig. 3. Most subjects who responded

Table 2 Prior procedures performed on study subjects

Infertile Category	Total # Patients	% Patients With Procedures	% Patients With Procedures + Sperm	FNA Mapping	MicroTESE
Azoospermia	26	24/26 (92%)	11/24 (46%)	22/26 (85%)	17/26 (65%)
Cryptozoospermia	4	3/4 (75%)	2/3 (66%)	2/4 (50%)	1/4 (25%)

Table 3 Isotretinoin response by male infertility category

Infertile Category	# Pts	# Pts with reliable ejaculated sperm	Median TMC ejaculated sperm
NOA w/prior procedure (+) sperm	8	2/8	110
NOA w/prior procedure (-) sperm	12	3/12	54
NOA w/prior cryptozoospermia	6	2/6	525
Cryptozoospermia	4	4/4	50

Note: NOA = Nonobstructive azoospermia; TMC = Total motile count

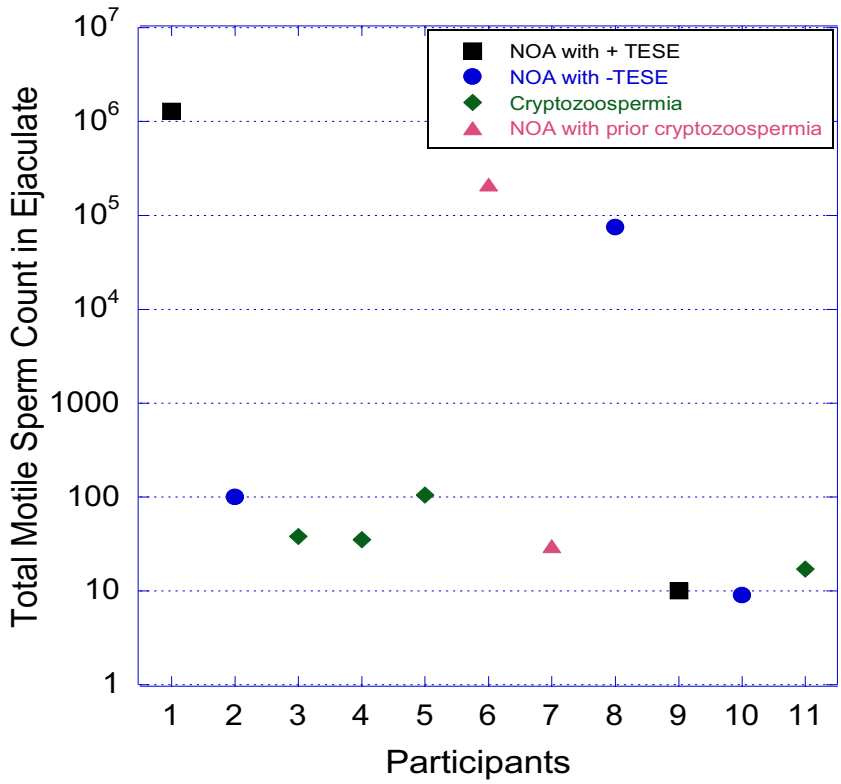

Fig. 2 Individual patient total motile sperm count (TMC) response to isotretinoin treatment. Values are means of the two highest measurements for each subject. Note y-axis is logarithmic and not linear in scale

to therapy did so within 3 months of initiating treatment. All those who responded at month three, and who continued with therapy, maintained their response through 6 and 9 months of therapy.

We also examined the response rate by testicular histology as assessed by testicular biopsy or FNA mapping prior to isotretinoin therapy (Table 4). Although not statistically significant (Fisher's exact p-value = 0.275 for the difference of proportions between the four groups), there was a trend toward better response as the level of germ cell maturation increased. We did not see a responder among the few patients with Sertoli cell-only histology patterns. However, among 11 subjects with early or late maturation arrest phenotypes, 50% and 60% respectively, responded to therapy.

Among men with azoospermia who did not develop sperm in their ejaculates, and who then proceeded to repeat sperm microdissection TESE retrieval procedures on isotretinoin, 6/7 (86%) had sufficient sperm found to cover

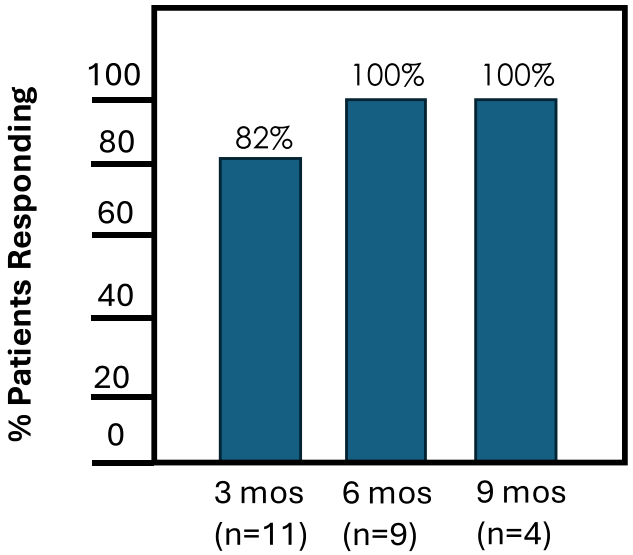

Fig. 3 Response times to achieve motile ejaculated sperm counts while on isotretinoin therapy in $n=11$ responding patients. Only $n=4$ patients remained on isotretinoin at 9 months. Note: mos = months

Table 4 Correlation of testis biopsy pattern with isotretinoin response

Testis Biopsy Pattern	# Patients	# Patients Responding
Sertoli cell only (SCO)	2	0/2 (0%)
Mixed (EMA, LMA, & SCO)	14	3/14 (21%)
Early Maturation Arrest	6	3/6 (50%)
Late Maturation Arrest	5	3/5 (60%)
TOTAL	27	9/27 (33%)

Note: SCO = Sertoli cell-only; EMA = Early maturation arrest; LMA = Late maturation arrest

all eggs at IVF-ICSI. In 5 of 7 cases (71%), sperm retrieval also generated sufficient sperm to cryopreserve for future IVF cycles. In addition, when comparing surgical times of prior microTESE procedures performed prior to isotretinoin therapy (mean 105 min; [range 75–150 min]) to those while on isotretinoin treatment (mean 63 min; [range 45–90 min]), they decreased by 40%.

To date, 9 IVF-ICSI cycles have been performed using ejaculated sperm in 6 complete responders. Thirteen euploid (e.g., biopsy normal) embryos have been generated with 1 live birth to date. Among partial responders having repeat sperm retrievals, 6 IVF-ICSI cycles have been performed with 1 pregnancy obtained. No spontaneous pregnancies have been observed as yet from treatment.

Side effects and complications

All 30 participants (100%) reported dry skin and chapped lips. Additional side effects included rashes 4/30 (13%), irritability 14/30 (47%), and altered cholesterol levels 5/30 (17%) (Table 1). One study subject dropped out of the study due to anxiety early in the study and is not included in the overall analysis.

Discussion

We observed that treatment with isotretinoin can lead to de novo sperm production in a significant proportion of men with nonobstructive azoospermia and cryptozoospermia. The success rate of 37% in achieving usable ejaculated sperm after RA treatment is preliminary but encouraging, especially considering the difficult-to-treat nature of patients with these conditions and the very strict definition applied for a successful outcome: Sufficient motile ejaculated sperm for use with IVF-ICSI. Interestingly, the magnitude of the response to isotretinoin therapy is similar to that ascribed to pre-adjuvant varicocelectomy (44%) in a systemic review and metanalysis of 15 studies of NOA patients [15]. The induction of ejaculated sperm was also demonstrated by treatment with letrozole in a randomized study of 11 NOA men [16] and in an early study of clomiphene citrate in 42 patients (64% ejaculated sperm) [17], but whether the induced ejaculated sperm was sufficient for IVF-ICSI with these treatments was not formally evaluated. Although many studies have reported on the variable ability of microTESE to find testicular sperm in cases of cryptozoospermia and prior failed microTESE procedures [18–21], our study is unique in that it defines successful sperm acquisition based on the finding of ejaculated sperm, which entirely obviates the need for microTESE procedures.

These findings align with prior pilot studies suggesting that RA plays a critical role in spermatogenesis [10, 11]. The importance of RA during spermiogenesis is further supported by the fact that our subjects with early and late maturation arrest responded the best (6/11 or 54%) to RA treatment. Thus, apparently a proportion of men with non-obstructive azoospermia and cryptozoospermia also harbor RA deficiencies that respond to supplementation in addition to the other underlying causes of their conditions.

The ability to induce ejaculated sperm production in men with severe male factor infertility has an obvious and immediate clinical benefit: It eliminates the need for invasive testicular sperm retrieval procedures. This not only reduces the substantial cost, effort, and complications inherent with TESE procedures, but also eliminates the high failure rate (50%) associated with these procedures. One underreported but consequential complication of TESE procedures is iatrogenic hypogonadism, which can substantially alter a patient's quality of life by requiring lifelong testosterone replacement [22]. RA treatment has the potential to eliminate this risk in this complex cohort of severely infertile men

who desire biological offspring. And, although our small study does not adequately address the quality of ejaculated sperm for IVF-ICSI, the generation of euploid embryos and ongoing pregnancies suggests no overarching concerns and aligns with a recent metanalysis concluding similar outcomes when cryptozoospermic and testicular sperm ICSI outcomes are compared [23]. The risks associated with RA treatment in this study include the substantial dermatological and possibly metabolic side effects and the 3–6 months of time needed to obtain ejaculated sperm on therapy.

This study is not without limitations. We acknowledge that since this is a single arm, uncontrolled trial, we cannot definitively state that the observed responses were due to isotretinoin treatment. In addition, the small sample size and the lack of a control group makes it difficult to apply statistical significance to our findings. The limited number of IVF-ICSI cycles performed during the study period likely reflects the significant effects of cost, planning, travel and other social factors that exist in treating this challenging population of infertile men. However, the clinical significance of this research is novel and significant if confirmed in larger studies. In the future, we aim to expand this series of patients and a) identify ideal candidates for isotretinoin therapy based on clinical characteristics and testis histology, b) optimize and timeline and dosage of RA treatment, and c) evaluate the effects of RA supplementation on sperm quality and fertility outcomes.

Retinoic acid supplementation with isotretinoin represents a promising therapeutic option for men with nonobstructive azoospermia and cryptozoospermia. By inducing ejaculated sperm in these patient cohorts, it obviates the need for complex and invasive sperm retrieval procedures.

Acknowledgements The authors would like to thank the clinical staff of The Turek Clinic for their valuable contributions to the care of study subjects.

Authors' contributions JKA and PJT conceived, designed and analyzed the research. CMJ performed and analyzed the research. CMJ and PJT wrote the manuscript.

Data availability Restrictions on data availability are necessary to protect human privacy, so no datasets are accessible at this time.

Declarations

Ethical approval This retrospective study involving human subjects was performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was reviewed and approved by the institutional review board (WCG IRB, Princeton, NJ; #1-1818243-1).

Conflict of interest JKA has research funding from Celldex Therapeutics and is a consultant for NEXT Life Sciences. CMJ and PJT are employees of The Turek Clinic and CMJ has no financial conflicts of interest. PJT owns stock in AlphaSperm, Inc and is on the medical advisory board of GiveLegacy Inc, Contraline Inc, Future Family Inc, Doximity Inc, Arex Bioscience Inc, and Inherent Bioscience Inc.

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