EJACULATED SPERM INDUCTION WITH ISOTRETINOIN IN AZOOSPERMIA AND CRYPTOZOOSPERMIA: WHO ARE THE LIKELY RESPONDERS?

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INTRODUCTION

- Retinoic acid (RA) is a metabolite of vitamin A critical for meiosis and mammalian spermatogenesis.
- We observed that RA supplementation with isotretinoin was associated with *de novo* ejaculated sperm counts in men with nonobstructive azoospermia (NOA) and cryptozoospermia.

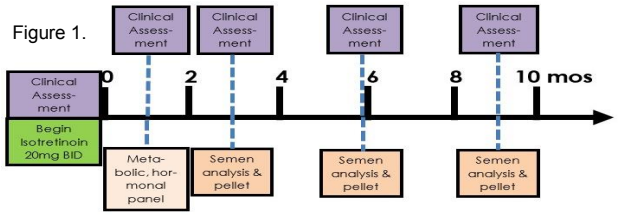
HYPOTHESIS

The best responders to isotretinoin treatment are those with evidence of spermatogenesis on biopsy histology or cytology.

OBJECTIVE

To determine which subsets of infertile men with NOA or cryptozoospermia are most likely to respond to isotretinoin treatment based on clinical and histological parameters.

Figure 1.



METHODS

- Single center, prospective, repeated measures analysis of infertile men given isotretinoin supplementation. All etiologies of infertility were included, as were subjects with prior sperm retrieval procedures.
- Clinical care pathway outlined in Figure 1.
- **Primary endpoint was the attainment of reliable, motile ejaculated sperm to proceed with IVF-ICSI**.
- Clinical characteristics, response rates and complications were analyzed descriptively. Fisher's exact test was used to assess correlations of sperm presence with infertility type and testicular histology or cytology.

RESULTS

Patient Demographics

- Among **n=30 subjects,** mean patient age was 38 years old.
- 26 were azoospermic and 4 were cryptozoospermic.
- 24/26 and 3/4 patients with NOA and cryptozoospermia had previously undergone testicular sperm retrieval or FNA mapping of testis procedures. (Table 1)

Table 1. Prior Procedures Performed on Study Subjects

Infertile Category	Total # Patients	% Patients w/ Procedures	% Patients w/ 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 2. Isotretinoin Response by Male Infertility Category

Infertile Category	# Pts	# Pts w/ 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

Table 3. 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 (EMA)	6	3/6 (50%)
Late Maturation Arrest (LMA)	5	3/5 (60%)
TOTAL	**27**	**9/27 (33%)**

RESULTS Cont.

- Overall, **37%** developed motile ejaculated sperm with isotretinoin treatment.
- **27%** of azoospermic and **100%** of cryptozoospermic men responded. (Table 2)
- Mean TMC achieved was 48,000 sperm. See Table 2 for median TMCs.
- **82%** subjects who responded to therapy, did so within 3 months of initiating treatment.
- Response rate by testicular histology shows trend toward better response as the level of germ cell maturation increased. (Table 3)
- 9 IVF-ICSI cycles using ejaculated sperm resulted in 13 euploid embryos and 1 live birth. 6 cycles using retrieved sperm has led to 1 pregnancy.
- All participants had dry skin and chapped lips, other side effects included irritability (47%), altered cholesterol (17%), & rashes (13%)

CONCLUSIONS

- Treatment with isotretinoin increases sperm production in men with NOA or cryptozoospermia to the point of obviating the need for testicular sperm retrieval procedures.
- Response to therapy correlates best with testis biopsy patterns showing evidence of early germ cells and germ cell maturation.
- Study limitations: small sample size and lack of controls.

REFERENCES

- Amory JK, Muller CH, and Walsh TJ. Isotretinoin for the treatment of nonobstructive azoospermia: a pilot study. Asian J Androl 2021; 23: 537–540.
- Amory JK, Ostrowski KA, Gannon JR, Berkseth K, Stevison F, Isoherranen N, Muller CH, and Walsh TJ. Isotretinoin administration improves sperm production in men with infertility from oligoasthenozoospermia: a pilot study. Andrology 2017; 5:1115–1123.