EJACULATED SPERM INDUCTION WITH ISOTRETINOIN IN AZOOSPERMIC AND CRYPTOZOOSPERMIC MEN: WHO ARE THE LIKELY RESPONDERS?

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Background: Retinoic acid (RA) is a metabolite of vitamin A critical for meiosis and mammalian spermatogenesis. In our pilot studies, we observed that RA supplementation with isotretinoin (13-cis retinoic acid) was associated with increased ejaculated sperm counts in some men with severe oligospermia and with the *de novo* presence of ejaculated sperm in men with nonobstructive azoospermia (NOA) and cryptozoospermia.

Objective: This analysis aimed 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.

Materials and Methods: Single center, prospective, repeated measures analysis of infertile men given isotretinoin supplementation. Infertile men with NOA or cryptozoospermia received isotretinoin (20mg twice daily) and had metabolic and semen evaluations over a minimum of 6 months. All etiologies of infertility (i.e. genetic or acquired) were acceptable for study inclusion, as were those with prior sperm retrieval procedures. The primary endpoint was attaining reliable total motile counts (TMC) of ejaculated sperm to proceed with IVF-ICSI.

Results: Among a consecutive series of n=27 men undergoing isotretinoin treatment for at least 6 months, 18 (67%) were azoospermic and 9 (33%) were cryptozoospermic at study intake. All azoospermic men and 6/9 (67%) of cryptozoospermic men had had prior sperm retrieval or FNA mapping procedures. Overall, 8/27 (30%) of study patients developed reliable, motile ejaculated sperm counts on isotretinoin. When considering clinical characteristics, including etiology, hormonal profiles and histopathological findings, testis biopsy patterns demonstrated the best correlation to isotretinoin response (Table).

Testis Biopsy Pattern	**# Pts**	**# Pts with reliable ejaculated sperm (%)**
Sertoli Cell Only	2	0/2
Mixed (SCO, EMA, LMA)	13	1/13 (8%)
Early Maturation Arrest (EMA)	4	2/4 (50%)
Late Maturation Arrest (LMA)	3	3/5 (60%)

Note: SCO = Sertoli cell only; EMA = early maturation arrest; LMA = late maturation arrest

Conclusions: Retinoic acid supplementation is associated with improved ejaculated sperm production in NOA and cryptozoospermic men. Response to therapy correlates best with testis biopsy pattern. Testes with maturation arrest patterns appear to respond best to isotretinoin. These findings agree with what is understood about the role of retinoic acid in mammalian spermatogenesis. Isotretinoin therapy may obviate the need for invasive testicular sperm retrieval procedures in cases of severe male factor infertility. Our findings that patients with maturation arrest histology patterns are the most likely to respond to therapy is encouraging as patients with this biopsy pattern are the most likely to fail TESE procedures.

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References

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