

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	3/3 (100%)

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

Source of Funding: None

MP18-13

PARADOXICAL RESPONSE TO CLOMIPHENE CITRATE IN MALE INFERTILITY: ONE OUT OF FOUR MEN EXPERIENCE SPERM COUNT DECLINE - FINDINGS FROM A REAL-LIFE CROSS-SECTIONAL STUDY

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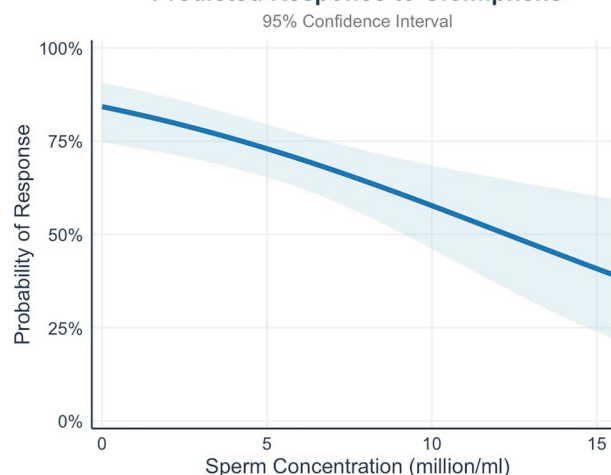
INTRODUCTION AND OBJECTIVE: Clomiphene citrate (CC) is a prescribed off-label SERM to treat hypogonadism in men with low sperm counts. Some men may experience a paradoxical decline in sperm count after starting CC. We aimed to investigate the frequency and predictive factors for this paradoxical response in men prescribed CC because of male factor infertility (MFI) at a tertiary academic center.

METHODS: Data from 166 men seeking first medical help for primary MFI with low sperm counts who were prescribed CC 50 mg QD, with a second semen analysis available at follow-up after treatment initiation, were analyzed. Sociodemographic, clinical characteristics, semen analysis and serum hormones were collected. Responders to CC were considered to be all those with an improvement in their sperm counts at follow-up semen analysis (after at least 3-mo of CC). Those who had a decline in sperm counts were considered non-responders. Descriptive statistics was used to detail the overall cohort and compare groups. Multivariate logistic regression analysis was used to explore potential predictors of responsiveness to CC.

RESULTS: Overall, the median (IQR) age was 37 (34-40) years. The median treatment duration was 4 (3-7) months. The baseline vs. follow-up median sperm concentration was 4.00 (1.42-8.00) vs. 5.60 (2.12-10.88) $\times 10^6/\text{mL}$, $p < 0.001$ and, total testosterone 3.19 (2.42-4.86) vs. 4.63 (3.69-5.83) ng/mL , $p = 0.02$, respectively. Responders were 118 (71.1%) and non-responders were 48 (28.9%). Responders had lower median baseline sperm concentration compared to non-responders: 3.20 (2.33-6.62) vs. 5.80 (3.77-9.81) $\times 10^6/\text{mL}$, $p = 0.003$, and reported higher BMI 25.68 (24.19-27.76) vs. 24.90 (23.22-26.78) kg/m^2 , $p = 0.04$. At multivariate logistic regression analysis, baseline lower sperm concentration was identified as predictive factor of being a responder to CC, OR: 0.87 (95% CI: 0.80-0.94) $p < 0.001$, after adjusting for baseline FSH, total testosterone, age and therapy duration. The probability of the logistic regression model is plotted over Figure 1

CONCLUSIONS: CC effectively increases both sperm concentration and total testosterone levels in most MFI men. Nevertheless, one out of four patient experience a paradoxical decline in sperm counts. Lower baseline sperm concentration was the only predictive factor for positive treatment response in terms of sperm concentration.

Predicted Response to Clomiphene



Source of Funding: None

MP18-14

GENETIC POLYMORPHISMS OF CYTOCHROME P450 2D6 (CYP2D6) ARE ASSOCIATED WITH HORMONAL AND SPERMATOGENIC RESPONSES TO ENCLMIPHENE THERAPY IN INFERTILE MEN

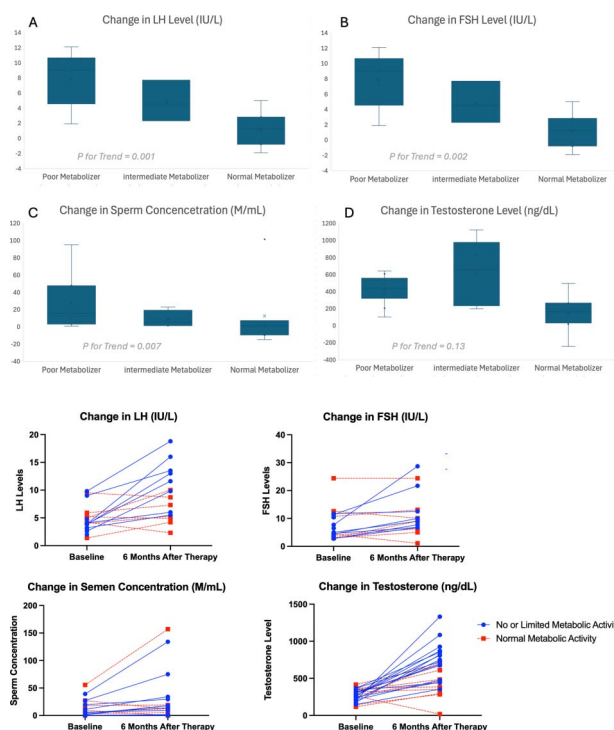
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INTRODUCTION AND OBJECTIVE: Clomiphene citrate is a mixture of two isomers, zuclophene and enclomiphene. Cytochrome P450 2D6 (CYP2D6) is the primary enzyme that metabolizes various medications; CYP2D6 inactivates enclomiphene. We hypothesize CYP2D6 genotype will predict differential response to clomiphene and enclomiphene among infertile men, with a greater response in those with a "poor metabolizer" variant.

METHODS: We included infertile men at a single institution who received whole genome sequencing and at least six months of clomiphene or enclomiphene therapy. CYP2D6 variants were classified according to PharmVar.org metabolizer phenotypes. Men taking strong CYP2D6 inhibitors (e.g. bupropion, sertraline, fluoxetine) were classified as poor metabolizers.

RESULTS: 26 men were included: 10 poor, 5 intermediate, and 11 normal metabolizers. Univariate analysis showed that poor metabolizers had the greatest improvements in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sperm concentration (Figures 1 and 2, $p < 0.05$). There was no statistical difference in testosterone level. Multivariate linear regression indicated that age, clomiphene vs enclomiphene use, baseline hormone levels and sperm concentration were not associated with response ($p > 0.05$), however, metabolizer status significantly predicted increases in LH, FSH, and sperm concentration ($p < 0.05$).

CONCLUSIONS: Infertile men who are poor metabolizers or take strong CYP2D6 inhibitors exhibit greater improvements in gonadotropins and sperm concentration when given enclomiphene therapy. This suggests that decreased clearance of enclomiphene in poor metabolizers leads to prolonged drug circulation and enhanced effects.



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MP18-15

COMPARING REBOOT PROTOCOL FOR RETURN OF SPERMATOGENESIS IN MEN ON TESTOSTERONE THERAPY WITH PRIOR VASECTOMY DESIRING FUTURE FERTILITY

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INTRODUCTION AND OBJECTIVE: Men with prior vasectomy and on concurrent testosterone therapy (TTh) are difficult to manage as semen analysis cannot be used to determine if sperm has returned to the ejaculate; they often require testicular biopsy (TESA) prior to proceeding with vasectomy reversal or sperm extraction for IVF. For men on TTh, human chorionic gonadotropin (hCG) plus a selective estrogen receptor modulator (SERM) have been used to reinduce spermatogenesis; more recent regimens have combined hCG+FSH for a "reboot." Men who previously fathered a child and then underwent vasectomy provide unique insight for reboot protocols after TTh, due to demonstration of prior fertility. The objective of this study is to compare efficacy of these two protocols (hCG+SERM vs hCG+FSH).

METHODS: Retrospective review of a single academic institution was performed to identify patients who 1) had a prior history of vasectomy, 2) were on TTh, 3) desired return of fertility and underwent a reboot protocol, and 4) had undergone TESA to assess for presence of sperm. All included men had demonstrated fertility prior to vasectomy. The two reboot protocols included: hCG 3000 IU three times weekly, plus either enclomiphene/clomiphene 25 mg daily or FSH 75 IU three times weekly. A negative control group of men who had undergone TESA while on concurrent testosterone therapy without a reboot protocol was also identified. Primary outcome was presence of sperm at the time of TESA. We also detailed whether men opted for vasectomy reversal or sperm retrieval with IVF/ICSI.

RESULTS: A total of 20 men were identified: 8 received hCG+SERM and 12 received hCG+FSH. Men had similar ages (49 vs 43 years, $p=0.70$) and duration since vasectomy (12 vs 13 years, $p=0.93$), respectively. All men had sperm identified on TESA. Median interval between the beginning of reboot therapy and TESA was 3

months in both groups ($p=0.07$, range 3-9 months). Two men in this cohort had a history of TESA or TESE while on testosterone (prior to reboot) at an outside institution with no sperm identified. Of 20 men, 10 men had successful TESE for IVF/ICSI, 5 underwent vasectomy reversals (all with return of sperm in the ejaculate), 2 have vasectomy reversals planned, 1 has a TESE planned, and 2 were no longer interested in fertility after TESA and restarted TTh.

CONCLUSIONS: Reinduction of spermatogenesis, or reboot, with either hCG+SERM or hCG+FSH appears to be successful, among men with proven prior fertility. This is the first series examining outcomes in men on TTh and with vasectomy. TESA at or after 3 months following initiation of reboot therapy is an effective measure to detect sperm prior to TESE or vasectomy reversal.

Source of Funding: None

MP18-16

ARTIFICIAL INTELLIGENCE AND INFERTILITY: ACCURACY, INCONSISTENCIES, AND CLINICAL IMPLICATIONS OF MISGUIDED RECOMMENDATIONS

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INTRODUCTION AND OBJECTIVE: Artificial intelligence has rapidly advanced to the center of academic discussions, with many studies assessing its accuracy in clinical care. However, limited information is available pertaining to the ramifications of inaccurate responses. This study is designed to assess not only ChatGPT's capacity to answer fertility questions in accordance with the American Urologic Association (AUA) guidelines for male infertility, but additionally the clinical ramification of inaccurate results.

METHODS: Each of the 54 statements from the AUA's Diagnosis and Treatment of Infertility in Men was adapted to prompt ChatGPT. Questions were presented as a general inquiry, a request for validation or further information, or a request for clinical next-step recommendations. Responses were categorized into three groups based on their adherence to the guidelines: accurate and complete (AC), accurate but incomplete (AI), and incorrect or misleading (IM). Non-AC responses were further classified into three subcategories: dangerous (D), mistreatment or misdiagnosis (MTMD), and unnecessary overtreatment (UOT).

RESULTS: Of ChatGPT's responses, 87% were categorized as AC, 4% as AI, and 9% as IM. Among the non-AC answers, 71% were MTMD, 29% were UOT, while notably 0% were D. Within the five categories of the guidelines, ChatGPT demonstrated the highest accuracy in Assessment, Lifestyle Factors, and Diagnosis/Evaluation. In contrast, accurate and complete concordance was lower for the Treatment category and lowest for the Imaging category. Most of the MTMD pertained to less common infertility conditions, such as Y-chromosome microdeletion analysis. Finally, the UOT answers often pertained to unnecessary ultrasound recommendations.

CONCLUSIONS: This study demonstrates ChatGPT's potential to provide accurate and reliable information in fertility care, particularly in assessment and diagnostic guidance. Importantly, non-AC responses were not found to be dangerous, but rather leading to misdiagnosis or overtreatment. Our findings underscore the importance both caution and intentional direction when querying AI for fertility related questions.