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

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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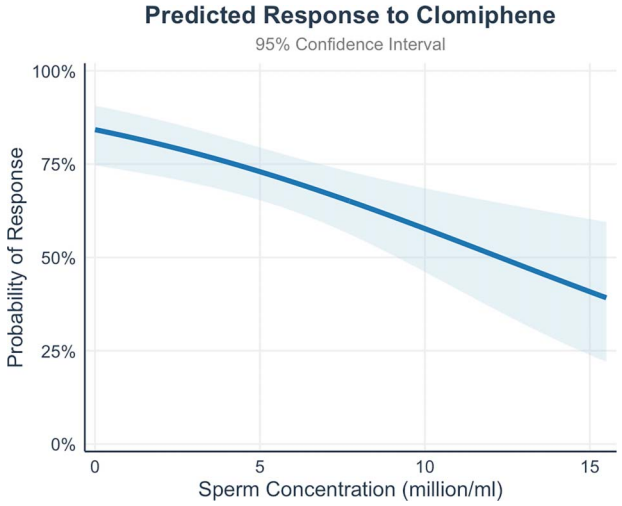
INTRODUCTION AND OBJECTIVE: Clomiphene citrate (CC) is a prescribed off-label SERM to treat hypogonadism in men with low sperm counts. Some men may experience a paradoxical decline in sperm count after starting CC. We aimed to investigate the frequency and predictive factors for this paradoxical response 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) x106/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) x106/mL, $p=0.003$, and reported higher BMI 25.68 (24.19-27.76) vs. 24.90 (23.22-26.78) kg/m2, $p=0.04$. 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.



Source of Funding: None

MP18-14

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

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INTRODUCTION AND OBJECTIVE: Clomiphene citrate is a mixture of two isomers, zuclomiphene 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.