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Early Versus Late Maturation Arrest: Reproductive Outcomes of Testicular Failure

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Abstract

Purpose—There is a paucity of data characterizing infertile men with maturation arrest. We hypothesized that men with early stage maturation arrest could be clinically distinguished from men with late maturation arrest and would have worse reproductive outcomes.

Materials and Methods—We retrospectively reviewed the records of all patients with nonobstructive azoospermia and cryptozoospermia who underwent testis mapping and sperm extraction from 2002 to 2009 and for whom histopathological findings were available. Patients had uniform maturation arrest if multiple biopsies revealed maturation arrest at the spermatogonia/spermatocyte (early maturation arrest) or the spermatid (late maturation arrest) stage. Clinical parameters and pregnancy outcomes of in vitro fertilization/intracytoplasmic sperm injection were examined. Statistical analysis consisted of univariate and multivariate analysis.

Results—Uniform maturation arrest was identified in 49 of 219 men (22.3%) undergoing testicular sperm extraction. On multivariate analysis men with maturation arrest had significantly larger testes ($p = 0.01$), decreased follicle-stimulating hormone ($p = 0.05$) and more detectable genetic abnormalities ($p = 0.01$) than men with other histopathological conditions. Men with late maturation arrest had decreased follicle-stimulating hormone ($p = 0.02$), increased testosterone ($p = 0.03$) and a higher sperm retrieval rate at testicular sperm extraction ($p = 0.01$) than men with early maturation arrest. Predictors of successful sperm retrieval were larger testes, cryptozoospermia, late maturation arrest and hypospermatogenesis (each $p \leq 0.05$). Pregnancy outcomes for men with maturation arrest were not significantly different from those for men with other histopathological conditions.

Conclusions—Maturation arrest is a common, diverse histopathological subtype of severe male infertility. Compared to men with late maturation arrest those with early maturation arrest have increased follicle-stimulating hormone, decreased testosterone and a decreased probability of mature spermatozoa. In vitro fertilization/intracytoplasmic sperm injection outcomes were similar when spermatozoa were discovered during testicular sperm extraction.

Keywords

testis; sperm maturation; infertility; male; azoospermia; biopsy

Nonobstructive azoospermia is characterized by absent sperm in the ejaculate, and cryptozoospermia occurs when a few sperm can be detected only after centrifugation and

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Study received institutional review board approval

pellet examination. The prevalence of azoospermia in the male population is approximately 1%, representing approximately 10% to 15% of infertile men.[1] Men with NOA represent the most challenging subset of infertile men to treat. Compared to fertile men they typically have increased FSH, decreased serum testosterone and decreased testicular volume. To initiate biological pregnancy they typically require IVF and ICSI using testicular or rare ejaculated sperm.[2]

Histopathological diagnoses based on testicular biopsies from men with NOA or cryptozoospermia include SCO, hypospermatogenesis and MA. MA is defined as germ cells that fail to complete maturation. Uniform MA is characterized by spermatogenic arrest at the same stage of spermatogenesis throughout the seminiferous tubules.[3] MA is subcategorized into early MA, in which only spermatogonia or spermatocytes are found, and late MA, in which spermatids are detected without spermatozoa.[4,5] Although spermatozoa are not visualized on histopathological evaluation, some men with MA may have small foci of spermatozoa in the testes that can be used for IVF/ICSI.[3]

Limited data exist to characterize men with MA. MA may be primary (genetic or idiopathic) or acquired. Acquired causes include iatrogenic conditions (chemotherapy, radiation, drugs and testosterone supplementation), nutrition, infection, endocrinopathy, congenital abnormalities (cryptorchidism), testicular torsion and varicocele.[6] Although men with MA are traditionally described as having normal serum FSH, LH, testosterone and prolactin,[7] Ishikawa et al found that those with later stages of MA had lower FSH and increased seminiferous tubule diameters than men with earlier stages of MA.[6] Men with MA were also reported to have more detectable genetic abnormalities, such as Y chromosome microdeletions and/or karyotypic abnormalities.[3,8–10] In 2009 Hung et al reported that men with uniform MA and normal FSH had a lower sperm retrieval rate with microTESE and worse IVF/ICSI outcomes than other men with NOA and cryptoozospermia.[3]

We further characterized MA by comparing multiple variables, hypothesizing that men with early MA can be clinically distinguished from men with late MA.

Materials and Methods

After receiving institutional review board approval we retrospectively reviewed the records of all men who underwent bilateral TESE at a single institution from 2002 to 2009. Patients were included in analysis if they had NOA or cryptozoospermia. Each patient was scheduled for IVF/ICSI at TESE or later if spermatozoa were detected. Men with motile or nonmotile sperm detected only after pellet centrifugation were considered to have cryptozoospermia. Men with cryptozoospermia underwent TESE if their reproductive endocrinologist requested testicular sperm due to nonviable ejaculated sperm. Men with fewer than 2 semen analyses, obstructive azoospermia or inadequate histopathological information were excluded from study.

Preoperatively each patient was thoroughly evaluated for infertility by a single urologist (LIL) according to the American Urological Association/American Society for Reproductive Medicine best practice statement.[11,12] This included a complete history and physical examination, 2 semen analyses with centrifugation and pellet analysis, and serum hormone analysis. Men with decreased testosterone (300 ng/ml or less) were medically treated with aromatase inhibitors, clomiphene citrate or human chorionic gonadotropin for at least 3 months before TESE to increase endogenous testosterone.[13–15] Testis volume is expressed as mean testis volume. Genetic analysis was done according to American Urological Association/American Society for Reproductive Medicine guidelines, consisting of routine

karyotype and Y chromosome microdeletion testing by multiplex polymerase chain reaction.[11]

Surgical sperm extraction was performed by bilateral site specific sextant testis biopsy, i.e. testis mapping, as previously described,[16] or by microTESE.[17] Each specimen, consisting of seminiferous tubules, was stored in Bouin's solution. A wet mount sample of each biopsy was examined under a phase contrast microscope for spermatozoa. If spermatozoa were not detected on manual dispersion, the tissue was reexamined after enzymatic dispersion with 0.1% collagenase. If spermatozoa were present, the sample was cryopreserved or used immediately for IVF/ICSI. If an abundant amount of spermatozoa was located in the first examined testis, biopsy of the contralateral testis was deferred.

A sample from each biopsy was also sent to an experienced pathologist for histopathological analysis.[18] Multiple tubules at multiple sites of each biopsy were examined using hematoxylin and eosin staining. Histopathological findings were classified as SCO by absent germ cells, as hypospermatogenesis by a decreased number of spermatozoa, as early MA by germ cells with arrest at the secondary spermatocyte, and as late MA by germ cells with spermatid arrest and without spermatozoa. Patients were determined to have uniform MA if the same level of spermatogenic development was noted throughout the seminiferous tubules examined. Men with combined SCO and MA were distinguished from those with uniform MA alone. If other mixed patterns were observed, the most advanced histopathological diagnosis from all specimens was used.

Four couples achieved pregnancy spontaneously or after intrauterine insemination. All other couples who elected biological pregnancy underwent IVF/ICSI. ICSI was done using testicular or rare ejaculated sperm.[19] The decision to use ejaculated sperm for IVF/ICSI was made by the physician performing IVF/ICSI. IVF/ICSI outcomes were reported from 2 major centers where most patients in this study underwent IVF/ICSI. Outcomes analyzed were fertilization rate, pregnancies per IVF/ICSI cycle and pregnancies per patient. Clinical pregnancy was defined as normal intrauterine pregnancy, as determined by transvaginal ultrasound and fetal heartbeat after 12 weeks of gestation.

Statistical analysis was performed using SPSS®, version 16.0. Univariate analysis consisted of Pearson's chisquare test for categorical variables, 1-way ANOVA or the independent t test for parametric continuous variables and the Wilcoxon rank sum or Kruskal-Wallis test for nonparametric continuous variables. Multivariate logistic regression was performed in a stepwise manner to create 3 models, including 1) variables associated with MA, 2) variables associated with late vs early MA and 3) variables associated with mature spermatozoa discovered on TESE. Variables were incorporated into the model if they showed $p \leq 0.10$ on univariate analysis. All tests were 2-sided with $p \leq 0.05$ considered statistically significant.

Results

Characteristics of Men Undergoing TESE

A total of 219 men underwent TESE from 2002 to 2009. Spermatozoa were detected in 49.3% of the men, of whom 85.4% had azoospermia and 14.6% had cryptozoospermia. Mean ± SD age was 34.8 ± 6.4 years. Mean followup was 14.4 months. Mean body mass index was 28.8 ± 5.8 kg/m^2, and 28.2% of the men were obese (body mass index 30 kg/m^2 or greater). Mean testis volume was 14.2 ± 4.1 ml. Mean serum FSH was 18.9 ± 14.6 mIU/ml, mean LH was 6.7 ± 4.9 mIU/ml, mean testosterone was 330.1 + 141.0 ng/ml and mean prolactin was 11.1 ± 9.4 ng/ml. Serum testosterone was 300 ng/ml or less in 48.1% of the men, of whom 79.8% were placed on medical treatment to improve endogenous testosterone with a mean improvement in serum testosterone from 245.2 to 464.9 ng/ml (paired t test p

<0.01). The sperm retrieval rate did not differ in men who did and did not receive medication (p = 0.47). Microscopic varicocelectomy was performed concomitantly in 26.9% of the men, which led to improved semen parameters in 32.0%.

In most of the men in our study the cause of infertility was idiopathic. Other causes of infertility were a history of malignancy in 10.5% of cases, cryptorchidism in 8.4% and epididymitis/orchitis in 5.5%. Y chromosome microdeletions were present in 8.0% of the patients, including 2, 3 and 9 with AZFb, AZFb,c and AZFc, respectively, and an abnormal karyotype was present in 13.2% (3.6% XXY). The incidence of genetic abnormalities was higher in men with combined SCO/MA and uniform MA (35.3% and 36.2%, respectively, p ≤0.05).

MA vs Other Histopathological Conditions

The characteristics of men categorized by histopathology varied (table 1). Compared to men with other subtypes those with uniform MA had increased testis volume, decreased FSH, LH and prolactin, and an increased frequency of genetic abnormalities on univariate analysis (p ≤0.05). On multivariate analysis men with uniform MA had increased testis volume (OR 1.3, 95% CI 1.1–1.5, p = 0.01), decreased FSH (OR 0.9, 95% CI 0.9–1.0, p = 0.05) and an increased frequency of genetic abnormalities (OR 4.6, 95% CI 1.5–14.7, p = 0.01).

Early vs Late MA

Compared to men with early MA those with late MA had increased testis volume, decreased FSH and LH, increased testosterone and an increased probability of spermatozoa extracted during TESE on univariate analysis (p ≤0.05, table 2). On multivariate analysis men with late MA had decreased FSH (OR 0.7, 95% CI 0.6–0.9, p = 0.03), increased testosterone (OR 1.1, 95% CI 1.0–1.1, p = 0.03) and an increased probability of spermatozoa extracted during TESE (OR 20.3, 95% CI 2.0–211.3, p = 0.01). Men with early MA were more likely to receive medication to improve endogenous testosterone than men with late MA (p = 0.02).

Men with late MA could also be distinguished from men with hypospermatogenesis. Besides a lower sperm retrieval rate (65.5% vs 90.1%, p <0.01), men with late MA had increased testicular size, decreased FSH and LH, and a higher frequency of genetic abnormalities (each p ≤0.05).

Variables and Spermatozoa Extracted at TESE

On univariate analysis, increased age, decreased FSH and LH, cryptozoospermia, late MA and hypospermatogenesis were associated with an increased probability of extracting spermatozoa during TESE (p ≤0.05, table 3). On multivariate analysis variables associated with successful sperm retrieval during TESE were increased testis volume (OR 1.1, 95% CI 1.1–1.2, p = 0.050), cryptozoospermia (OR 18.8, 95% CI 3.8–92.4, p <0.01), late MA (OR 3.1, 95% CI 1.1–9.4, p = 0.05) and hypospermatogenesis (OR 36.4, 95% CI 10.3–128.9, p <0.01). The sperm retrieval rate did not statistically differ between testis mapping and microTESE (49.5% and 45.0%, respectively, p = 0.69).

Reproductive Outcome

After microscopic varicocelectomy 2 couples achieved spontaneous pregnancy and 2 achieved pregnancy using intrauterine insemination. Each patient had a significant improvement in semen parameters after varicocelectomy. Of the 108 couples with sperm extracted during TESE 56 underwent IVF/ICSI with a 29.2% pregnancy rate per cycle. During followup 7 couples pursued IVF/ICSI elsewhere, 21 used donor sperm to achieve pregnancy, 7 elected adoption, 9 deferred IVF/ICSI due to expense and 2 divorced. Many couples were contemplating IVF/ICSI at last followup.

When categorized by histopathological findings, IVF/ICSI outcomes did not differ significantly. Pregnancy was achieved at a rate of 33.3% per IVF/ICSI cycle by patients with MA and at 26.8% per cycle by those with another histopathological condition ($p = 0.46$). The pregnancy rate per IVF/ICSI cycle was 33.3% for men with early and late MA ($p = 1.0$). Fertilization and implantation results also did not significantly differ by histopathological findings ($p > 0.05$). The IVF/ICSI pregnancy rate using ejaculated vs testicular sperm did not differ significantly ($p = 0.71$). Of the men for whom ejaculated sperm was used for IVF/ICSI 66% had azoospermia before varicocelectomy. Frozen testicular sperm was used for IVF/ICSI on 2 occasions, resulting in 1 clinical pregnancy.

Discussion

Multiple studies describe variables associated with the detection of spermatozoa during TESE in men with NOA. Although some groups reported that FSH, LH, testosterone, testis volume and genetic abnormalities are associated with sperm detection during TESE, others reported no difference.[20,21] In 2004 Samli and Dogan created an artificial neural network to predict the probability of sperm detection during TESE.[22] The network predicted the TESE outcome in 59 of 73 men, compared to a logistic regression model, which predicted the outcome in 48 men ($p = 0.07$).[22] In our study increased testicular volume, cryptozoospermia and favorable histopathology (late MA and hypospermatogenesis) independently predicted sperm detection during TESE.

A relationship between favorable histopathological findings and spermatozoa during TESE was previously noted. More advanced histopathological results, such as MA and hypospermatogenesis, have correlated with the detection of spermatozoa during initial and repeat TESE.[23,24] Favorable testicular histopathology, such as late MA and hypospermatogenesis, may also influence the therapeutic effects of clomiphene citrate[15] and varicocele repair.[25]

A paucity of clinical evidence exists comparing the different stages of spermatogenic arrest. In our study multivariate analysis revealed that men with late MA had decreased FSH, increased testosterone and an increased probability of sperm recovery. Although each group had relatively high sperm retrieval rates, men with late MA and hypospermatogenesis could also be differentiated. Compared to men with hypospermatogenesis who commonly have complete spermatogenesis in focal areas of the testes, men with late MA had increased testicular volume, decreased FSH and LH, increased genetic abnormalities and a decreased sperm retrieval rate, likely indicating incomplete spermatogenesis diffused throughout the testes.

We also confirmed other reports that men with MA have an increased frequency of detectable genetic abnormalities.[3,8–10] Although the number of Y chromosome microdeletions and overall genetic abnormalities was significantly greater in men with MA, the number of karyotype abnormalities was not. This likely occurred since all men with Klinefelter's syndrome had SCO or hypospermatogenesis. Detectable genetic abnormalities were similar in men with early and late MA.

Although men with early MA are believed to have defects in meiotic recombination, karyotype abnormalities or Y chromosome abnormalities might lead to other defects in spermatogenesis. Since it was estimated that genetic abnormalities cause or contribute to infertility in 50% of infertile men[26] and approximately 50% of the men in our cohort had idiopathic infertility, many genetic defects escape detection with current testing.

The limitations of this study include its retrospective design. A prospective study should be done to validate our results. Although a large number of patients participated in this study,

few had uniform MA. Since many men in whom sperm were detected during TESE elected not to pursue IVF/ICSI, the analysis of reproductive outcomes may have been underpowered. Reasons for not proceeding with IVF/ICSI included financial cost and concerns of transmitting genetic abnormalities to their offspring.

The sperm retrieval method is also associated with differing success rates.[27] Some evidence suggests that microTESE is superior to other techniques[28] but variation in surgical techniques among surgical centers makes direct comparison difficult, precluding the recommendation of 1 technique.

Variability in the interpretation of testis histopathology must also be mentioned.[29] Performing multiple biopsies per testicle permitted the histological evaluation of multiple testicular regions and likely improved the accuracy of interpretation. Despite mixed histology in some samples we used the most advanced diagnosis that we believe best correlated with spermatozoa detection. Testicular biopsy is not a complete evaluation of testicular function and other clinical variables should be considered when evaluating a man with NOA.

Conclusions

MA is a common histopathological subtype in men with NOA and cryptozoospermia. Multiple clinical variables can distinguish men with uniform MA from those with other histopathological conditions, including increased testicular volume, lower FSH and detectable genetic abnormalities. When men with uniform MA were subcategorized, those with late MA had significantly decreased FSH, increased testosterone and a higher probability of extracting spermatozoa during TESE. Variables associated with the detection of spermatozoa during TESE included increased testis volume, cryptozoospermia and favorable histopathological findings. If testicular sperm was detected, pregnancy outcomes did not differ by histopathological results. This information can be used to counsel men with NOA or cryptozoospermia and their partners when deciding on treatment.

Acknowledgments

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Abbreviations and Acronyms

FSH	follicle-stimulating hormone

ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilization
LH	luteinizing hormone
MA	maturation arrest
microTESE	microdissection TESE
NOA	nonobstructive azoospermia
SCO	Sertoli's-cell only
TESE	testicular sperm extraction

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Table 1

Patient histopathological characteristics

	SCO	SCO/MA	Uniform MA	Hypospermatogenesis	Overall		p Value
No. pts	76	21	49	69	219		
% Cryptozoospermia	2.6	14.3	24.5	22.5	14.6	<0.01	
Mean ± SD age	33.9 ± 5.4	35.0 ± 9.0	34.9 ± 6.7	35.8 ± 6.2	34.8 ± 6.4	0.52	(1-way ANOVA)
Mean ± SD body mass index (kg/m^2)	29.1 ± 6.1	29.3 ± 5.4	29.2 ± 3.9	28.1 ± 6.1	28.8 + 5.8	0.61	(1-way ANOVA)
Mean ± SD testis vol (ml)	12.8 ± 4.2	13.0 ± 4.0	16.3 ± 2.8	15.1 ± 3.6	14.2 ± 4.1	<0.01	(1-way ANOVA)
Mean ± SD FSH (mIU/ml)	27.4 ± 15.3	23.9 ± 8.8	10.3 ± 7.6	14.3 ± 12.8	18.9 ± 14.6	<0.01	(Kruskal-Wallis test)
Mean ± SD LH (mIU/ml)	9.4 ± 6.5	8.7 ± 4.7	4.9 ± 3.4	6.5 ± 4.8	6.7 ± 4.9	<0.01	(Kruskal-Wallis test)
Mean ± SD testosterone (ng/dl)	338 ± 167	272 ± 93	334 ± 108	333 ± 142	330 ± 131	0.12	(Kruskal-Wallis test)
Mean ± SD prolactin (ng/ml)	12.7 ± 9.3	10.6 ± 5.4	8.0 ± 3.7	10.6 ± 10.3	11.1 ± 9.4	0.07	(Kruskal-Wallis test)
% Idiopathic infertility	50.0	52.4	52.1	49.3	50.5	0.97	(Pearson's chi-square test)
% Y chromosome microdeletion	1.6	17.6	21.4	1.9	8.0	<0.01	(Pearson's chi-square test)
% Abnormal karyotype	13.6	20.0	18.1	3.9	13.2	0.13	(Pearson's chi-square test)
% Genetic abnormality	15.1	35.3	36.2	5.9	19.6	<0.01	(Pearson's chi-square test)
% Spermatozoa on TESE	14.1	38.1	51.0	90.1	49.3	<0.01	(Pearson's chi-square test)

Table 2

Univariate and multivariate analyses of patients with early vs late MA

	Univariate			Multivariate	
	Early MA	**Late MA**	**p Value**	**OR (95% CI)**	**p Value**
No. pts	20	29			
% Cryptozoospermia	10.0	34.5	0.11		
Mean ± SD age	37.2 ± 8.2	33.4 ± 5.1	0.06		
Mean ± SD body mass index (kg/m^2)	28.9 ± 5.1	29.7 ± 5.7	0.66		
Mean ± SD testis vol (ml)	15.2 ± 2.5	17.1 ± 2.6	0.02	1.4 (0.9–2.1)	0.10
Mean ± SD FSH (mIU/ml)	15.2 ± 9.2	7.0 ± 3.8	<0.01	0.7 (0.6–0.9)	0.02
Mean ± SD LH (mIU/ml)	6.2 ± 4.0	4.0 ± 2.7	0.04		
Mean ± SD testosterone (ng/dl)	285.7 ± 82.8	367.1 ± 111.2	0.01	1.1 (1.0–1.1)	0.03
% Medication before TESE	75	37.9	0.02		
Mean ± SD prolactin (ng/ml)	10.1 ± 5.5	7.6 ± 3.5	0.11		
% Idiopathic infertility	47.4	55.2	0.60		
% Y chromosome microdeletions	31.3	15.4	0.27		
% Abnormal karyotype	11.1	23.1	0.44		
% Genetic abnormality	36.9	35.7	0.94		
% Spermatozoa on TESE	30.0	65.5	0.02	20.3 (2.0–211.3)	0.01

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Table 3

Probability of finding mature spermatozoa during TESE

	Univariate			Multivariate	
	No Sperm	**Sperm**	**P Value**	**OR (95% CI)**	**p Value**
No. pts	111	108			
Mean ± SD age	34.0 ± 6.4	35.7 ± 6.3	0.04	1.1 (1.0–1.1)	0.10
Mean ± SD body mass index (kg/m-)	28.3 ± 5.8	29.3 ± 5.7	0.21		
Mean ± SD testis vol (ml)	14.0 ± 4.1	14.9 ± 3.9	0.09	1.1 (1.1–1.2)	0.05
Mean ± SD FSH (mIU/ml)	22.7 ± 15.3	15.4 ± 12.4	<0.01	1.0 (0.9–1.0)	0.50
Mean ± SD LH (mIU/ml)	8.4 ± 6.1	6.2 ± 4.4	<0.01	0.9 (0.8–1.0)	0.21
Mean ± SD testosterone (ng/dl)	318.7 ± 147.3	337.7 ± 134.1	0.22		
% Medication before TESE	47.3	52.7	0.47		
Mean ± SD prolactin (ng/ml)	11.2 ± 8.2	10.5 ± 8.5	0.30		
% Idiopathic infertility	51.8	48.2	0.69		
% Y chromosome microdeletions	50.0	50.0	1.0		
% Abnormal karyotype	59.1	40.9	0.49		
% Genetic abnormality	55.6	44.4	0.63		
% Cryptozoospermia	6.1	93.9	<0.01	18.8 (3.8–92.4)	<0.01
% Sperm retrieval technique:			0.69		
Testis mapping	50.5	49.5			
MicroTESE	55.0	45.0			
% Histopathological findings:					
Sertoli's-cell only	81.2	18	Referent	Referent	
Early maturation arrest	70.0	30.0	0.17	1.8 (0.5–6.3)	0.39
Late maturation arrest	34.5	65.5	0.02	3.1 (1.1–9.4)	0.05
Hypospermatogenesis	11.1	88.9	<0.01	36.4 (10.3–128.9)	<0.01