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·Original Article·

Predictors for partial suppression of spermatogenesis of hormonal male contraception

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Abstract

Aim: To analyze factors influencing the efficacy of hormonal suppression of spermatogenesis for male contraception. **Methods:** A nested case-control study was conducted, involving 43 subjects, who did not achieve azoospermia or severe oligozoospermia when given monthly injections of 500 mg testosterone undecanoate (TU), defined as partial suppressors compared with 855 subjects who had suppressed spermatogenesis (complete suppressors). Sperm density, serum testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations at the baseline and the suppression phase were compared between partial and complete suppressors. Polymorphisms of androgen receptor (AR) and three single nucleotide variants and their haplotypes of FSH receptor (FSHR) genes determined by polymerase chain reaction (PCR) and DNA sequencing technique were compared between 29 partial and 34 complete suppressors. **Results:** Baseline serum LH level was higher and serum LH as well as FSH level during the suppression phase was less suppressed in partial suppressors. Additionally, in a logistic regression analysis larger testis volume, higher serum FSH concentrations alone, or interaction of serum LH, FSH, testosterone and sperm concentrations were associated with degree of suppression. The distribution of polymorphisms of AR or FSH receptor genes did not differ between partial and complete suppressors. In cases with incomplete FSH suppression (FSH > 0.2 IU/L), the chances of reaching azoospermia were 1.5 times higher in the subjects with more than 22 CAG triplet repeats. **Conclusion:** Partial suppression of spermatogenesis induced by 500 mg TU monthly injections is weakly influenced by hormonal and clinical features but not polymorphism in AR and FSHR genes. *(Asian J Androl 2008 Sep; 10: 723–730)*

Keywords: male contraception; genetic polymorphism; androgen receptor; CAG repeats; follicle stimulating hormone receptor; single nucleotide polymorphism; sperm concentration

1 Introduction

The goal of hormonal male contraception is induction of azoospermia or severe oligozoospermia to the levels required for reliable prevention of pregnancy [1–3]. However, the heterogeneity response of subjects to hor-

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monal suppression of spermatogenesis remains an unresolved problem. Despite marked and sustained suppression of serum gonadotrophins, suppression of spermatogenesis is incomplete in a minority of subjects in most studies. Such variability in response is significant between and within ethnic groups [4, 5], and is a key issue influencing clinical efficacy, general acceptability and wider applicability of hormonal male contraceptives.

While seeking an explanation for the variability in response, previous studies have revealed differences in pretreatment hormone values [6, 7], intratesticular testosterone (T) metabolism [8] and in the sensitivity of the pituitary-hypothalamic feedback system to exogenous T [9, 10]. In recent years an increasing body of evidence has shown that individual response to drug therapy at the molecular level is in part determined by genetic polymorphism, resulting in subtle differences in protein action or drug metabolism [11].

Based on previous findings, the potential factors that might influence the efficacy of hormonal male contraception, including clinical parameters, hormone values and genetic polymorphism in androgen receptor (AR) and follicle stimulating hormone receptor (FSHR), were measured and assessed in the present nested case-control study to identify predictors of partial (or incomplete) suppression of spermatogenesis with hormonal male contraception.

2 Materials and methods

2.1 Clinical protocol

The contraceptive efficacy study was an open-label, multicenter, phase III clinical trial with World Health Organization (WHO) standard monitoring, and consisted of a 2-month baseline period prior to a 30-month treatment period and a 12-month recovery period. The study enrolled 1 045 healthy fertile Chinese men, aged 20–45 years, from 10 family planning service centers throughout China. After screening of participants and their partners for eligibility, subjects entered the treatment period and received monthly injections of testosterone undeconate (TU) in 500 mg doses for up to 6 months (suppression phase) followed by a 24-month efficacy phase. Injections were administered and recorded by research nurses at each center. Injections outside a time window of 2 days were considered missed. During the suppression phase 190 subjects discontinued the trial, including 43 subjects who failed to reach azoospermia or severe oligozoospermia ($\leq 1 \times 10^6$/mL) and were defined as partial suppressors, while 855 subjects who had suppressed spermatogenesis ($\leq 1 \times 10^6$/mL) were defined as complete suppressors and met entry criteria of the efficacy phase. During the efficacy phase no other form of contraception except monthly injections of TU at doses of 500 mg were allowed and subjects underwent general physical and andrological examination, provided semen and fasting blood samples at 3 monthly intervals before each TU injection for reproductive hormones and biochemistry assays. During the recovery period, subjects were also asked to attend the clinic for physical examinations and to provide semen and fasting blood samples at 3 monthly intervals for 12 months. Couples were advised to use a reliable contraceptive method if they wanted to avoid pregnancy.

Written informed consent was obtained from the participants and their partners at entry into the trial. The study and consent form were approved by the Ethics Committee and Institutional Review Board of each participating center as well as the Scientific and Ethical Review Group of the WHO Human Reproduction Programme.

2.2 Subjects received assay of genetic polymorphisms

The assay for genetic polymorphisms was a nested case-control study. A total of 63 subjects, including 29 partial and 34 complete suppressors who matched partial suppressors in clinical features, provided blood samples for polymorphic assay of AR and FSHR genes after informed consent and were allocated to the test and the control group, respectively.

2.3 Measurements

Semen analyses were performed according to the WHO laboratory manual [12]. Azoospermia was defined as absence of sperm from seminal fluid smear after centrifugation at 3 000 × *g* for 15 min. Severe oligozoospermia was defined as sperm concentrations of 1×10^6/mL or less. Testis volume was estimated using Prader's orchidometer with measurements combined to calculate the total testis volume. Serum samples were measured together in batches in the central laboratory of the Beijing Coordinating Center. Serum T, luteinizing hormon (LH) and follicle stimulating hormone (FSH) were assayed using commercial kits supplied by Immunometrics (London, UK) [5]. The assay sensitivities were 0.35 nmol/L, 0.1 IU/L and 0.2 IU/L for T, LH and FSH, respectively. The mean intra-assay coefficients of variation for serum T, LH and

FSH were 7.1%, 3.4% and 3.2%, respectively. The mean inter-assay coefficient of variation for serum T, LH and FSH were 15.4%, 7.5% and 7.8%, respectively.

2.4 DNA isolation and polymorphic analysis

Genomic DNA was isolated from peripheral blood samples using kits according to the manufacturer's instructions. The number of CAG triplet repeats in AR and the single nucleotide polymorphism (SNP) in FSHR genes were determined by polymerase chain reaction (PCR) and using a DNA sequencing technique following previous research [13–16].

2.5 Statistics

Statistical analyses were performed using SPSS software package for windows (version 13.0; SPSS, Chicago, IL, USA). All parameters in the present study were tested for normal distribution. Sperm concentration, serum LH and FSH data that were not normally distributed were logarithm-transformed before analysis. Logistic regression modeling with backward stepwise (likelihood ratio) criterion was used to assess the variables affecting the suppression of spermatogenesis. Independent samples *t*-test and one-way analysis of variance (ANOVA) were used to compare differences after logarithm transformation. The χ^2-test was used to compare frequencies. Descriptive statistics were given as either mean ± SEM/SD or median together with minimum and maximum. All hypothesis tests were two-tailed. $P < 0.05$ was considered significant.

3 Results

3.1 Analyses of clinical parameters, sperm density and hormone values

Baseline serum LH was significantly higher among partial suppressors, whereas there was no significant difference at the baseline of age, body mass index (BMI), total testis volume, sperm density, serum T and FSH levels between partial and complete suppressors. During the suppression phase, serum LH and FSH levels were significantly less suppressed in partial compared with complete suppressors (Table 1).

Logistic regression analysis showed that larger testis volume ($P = 0.002$, Exp$\beta = 0.82$), higher serum FSH concentrations either at the baseline ($P = 0.032$, Exp$\beta = 0.47$) or at the suppression phase ($P = 0.002$, Exp$\beta = 0.000$) alone, or interaction of serum LH concentrations at the baseline by BMI ($P = 0.022$, Exp$\beta = 0.99$), serum T concentrations at the baseline by sperm concentrations at the baseline ($P = 0.014$, Exp$\beta = 0.99$), and serum FSH concentrations at the baseline by serum FSH concentrations at the suppression phase ($P = 0.019$, Exp$\beta = 1.15$) were associated with greater risk of partial suppression of spermatogenesis.

3.2 The number of CAG triplet repeats within exon 1 in androgen receptor gene

The distribution of CAG triplet repeat lengths was virtually identical in partial and complete suppressors (Figure 1), with no significant difference in the mean

Table 1. Clinical characteristics before testosterone undeconate (TU) treatment and concentrations of serum reproductive hormones between complete and partial suppressors. Data are expressed as mean ± SEM. BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone.

Parameters	Complete suppressors (n = 855)	Partial suppressors (n = 43)	P-value
Age (years)	32.9 ± 0.1	33.1 ± 0.6	0.808
BMI	22.7 ± 0.1	22.1 ± 0.3	0.105
Total testis volume (mL)	35.5 ± 0.2	34.2 ± 0.9	0.167
Sperm density (10^6/mL)	59.4 ± 1.0	53.7 ± 3.5	0.202
T (nmol/L) at baseline	17.6 ± 0.2	18.4 ± 0.8	0.407
T (nmol/L) at suppression phase	23.9 ± 0.3	23.7 ± 1.4	0.925
LH (IU/L) at baseline	3.75 ± 0.10	4.53 ± 0.40	0.005
LH (IU/L) at suppression phase	0.20 ± 0.01	0.49 ± 0.10	0.004
FSH (IU/L) at baseline	5.33 ± 0.10	5.14 ± 0.40	0.442
FSH (IU/L) at suppression phase	0.29 ± 0.03	0.67 ± 0.10	0.004

Table 2. Distribution of follicle stimulating hormone receptor (FSHR) genotype at nucleotide position –29, amino acid position 307 and 680 in the test group and the control group. A, Adenine; G, Guanine; Thr, Threonine; Ala, Alanine; Asn, Asparagine; Ser, Serine.

Group	Position –29			Position 307			Position 680		
	AA (%)	AG (%)	GG (%)	Thr/Thr (%)	Thr/Ala (%)	Ala/Ala (%)	Asn/Ser (%)	Ser/Ser (%)	Asn/Asn (%)
Test (n = 29)	20.7	55.2	24.1	48.3	37.9	13.8	48.3	37.9	13.8
Control (n = 34)	32.4	38.2	29.4	50.0	44.1	5.9	52.9	38.2	8.8

Table 3. Serum follicle stimulating hormone (FSH) levels (IU/L) at the baseline among FSH receptor (FSHR) genotypes in the test group and the control group. Data are expressed as mean ± SD. A, Adenine; G, Guanine; Thr, Threonine; Ala, Alanine; Asn, Asparagine; Ser, Serine.

Group	Position –29			Position 307			Position 680		
	AA (IU/L)	AG (IU/L)	GG (IU/L)	Thr/Thr (IU/L)	Thr/Ala (IU/L)	Ala/Ala (IU/L)	Asn/Asn (IU/L)	Asn/Ser (IU/L)	Ser/Ser (IU/L)
Test (n = 29)	6.0 ± 1.6	5.7 ± 2.4	5.7 ± 1.8	5.3 ± 1.2	6.6 ± 3.1	5.5 ± 0.6	5.3 ± 1.2	6.6 ± 3.1	5.5 ± 0.6
Control (n = 34)	5.2 ± 2.4	7.5 ± 4.4	5.2 ± 3.1	6.4 ± 3.8	5.1 ± 2.9	10.3 ± 4.4	6.2 ± 3.8	5.2 ± 3.0	8.9 ± 3.9

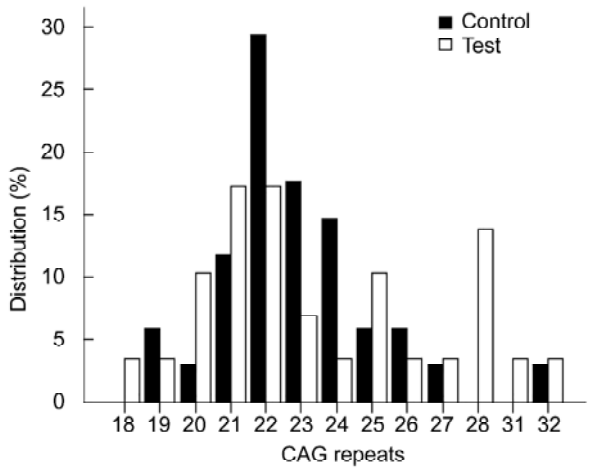

Figure 1. Distribution of androgen receptor gene exon 1 CAG genotype between the test (n = 29) and the control group (n = 34).

Table 4. Allelic frequency of the four follicle stimulating hormone receptor (FSHR) haplotypes in the test group and control group. [a]Indicating the number of single strand DNA. A, Adenine; G, Guanine; Thr, Threonine; Ala, Alanine; Asn, Asparagine; Ser, Serine.

Allele (–29/307/680)	Test group (n = 29)		Control group (n = 34)	
	%	n^a	%	n^a
A-Thr-Asn	27.6	16	32.4	22
A-Ala-Ser	6.9	4	8.8	6
G-Thr-Asn	25.9	15	30.9	21
G-Ala-Ser	12.1	7	10.3	7
Undecided	27.6	16	17.6	12
Total	100.0	58	100.0	68

repeat length between the test group (23.6 ± 3.6, range: 18–32) and the control group (23.0 ± 2.4, range: 19–32). However, subjects with CAG triplet repeats numbering more than 22 had a chance of achieving azoospermia 1. 5 times higher than that in cases with incomplete FSH suppression (FSH > 0.2 IU/L).

3.3 Single nucleotide polymorphisms (SNPs) of FSHR at nucleotide position –29 (FSHR promoter), amino acid position 307 and 680 (exon 10)

The distribution of FSHR genotype at nucleotide position –29, amino acid position 307 and 680 in both the test group and the control group is summarized in Table 2. There was no significant difference in the frequency of distribution among the genotype ($P > 0.05$, χ^2-test). The serum FSH concentrations at the baseline among FSHR genotypes are shown in Table 3. No significant difference in serum FSH concentrations at the baseline among the FSHR genotypes either in the test group or the control group was noted ($P > 0.05$, ANOVA).

3.4 FSHR haplotypes

The overall frequency of four FSHR haplotypes in the two groups is listed in Table 4. No significant difference in frequency of distribution between the two

Table 5. Allele combination, genotype distribution, and serum follicle stimulating hormone (FSH) levels at the baseline in the test group (n = 29). Data are expressed as mean ± SD. [a]Not possible to discriminate between the two possible allele combinations. A, Adenine; G, Guanine; Thr, Threonine; Ala, Alanine; Asn, Asparagine; Ser, Serine.

Group	Allele combination (–29/307/680)	Frequency (%)	(n)	FSH (IU/L)
1	A-Thr-Asn/A-Thr-Asn	17.2	5	5.4 ± 0.8
2	A-Thr-Asn/A-Ala-Ser	3.4	1	9.0
3	A-Ala-Ser/A-Ala-Ser	0	0	0
4	A-Thr-Asn/G-Thr-Asn	17.2	5	4.8 ± 1.5
5[a]	A-Thr-Asn/G-Ala-Ser or G-Thr-Asn/A-Ala-Ser	27.6	8	6.4 ± 3.4
6	A-Ala-Ser/G-Ala-Ser	10.3	3	5.5 ± 0.8
7	G-Thr-Asn/G-Thr-Asn	13.8	4	5.6 ± 1.5
8	G-Thr-Asn/G-Ala-Ser	6.9	2	6.0 ± 3.6
9	G-Ala-Ser/G-Ala-Ser	3.4	1	5.6

Table 6. Allele combination, genotype distribution, and serum follicle stimulating hormone (FSH) levels at the baseline in the control group (n = 34). Data are expressed as mean ± SD. [a]Not possible to discriminate between the two possible allele combinations. A, Adenine; G, Guanine; Thr, Threonine; Ala, Alanine; Asn, Asparagine; Ser, Serine.

Group	Allele combination (–29/307/680)	Frequency (%)	(n)	FSH (IU/L)
1	A-Thr-Asn/A-Thr-Asn	17.6	6	5.1 ± 2.5
2	A-Thr-Asn/A-Ala-Ser	11.8	4	6.1 ± 2.3
3	A-Ala-Ser/A-Ala-Ser	0	0	0
4	A-Thr-Asn/G-Thr-Asn	17.6	6	9.1 ± 5.0
5[a]	A-Thr-Asn/G-Ala-Ser or G-Thr-Asn/A-Ala-Ser	11.8	4	4.0 ± 1.8
6	A-Ala-Ser/G-Ala-Ser	5.9	2	10.3 ± 4.5
7	G-Thr-Asn/G-Thr-Asn	14.7	5	4.9 ± 1.5
8	G-Thr-Asn/G-Ala-Ser	14.7	5	5.5 ± 4.3
9	G-Ala-Ser/G-Ala-Ser	0	0	0

groups was found ($P > 0.05$, χ^2-test). These four haplotypes accounted for 77.8% of the FSHR alleles of the two groups and combined into the 10 major combinations shown in Tables 5 and 6, in which only nine groups were presented because two possible allelic combinations in group 5 (double heterozygous) could not be distinguished and considered together. The distribution of genotype between the test and the control group was not significantly different ($P > 0.05$, χ^2-test). No significant difference in the FSH levels at the baseline among the FSHR genotype either in the test group or in the control group was found (Tables 5 and 6). In addition, a correlation between genotypes and FSH concentrations at the baseline was not found in the present study either.

4 Discussion

In this study, we used 500 mg TU monthly injections alone in over 1 000 healthy fertile Chinese men. Among these, 43 subjects remained partial suppressors in failing to achieve either azoospermia or severe oligozoospermia within a 6-month suppression phase comprising a 4.7% rate of only partial suppression by cumulative life-table analysis (data not shown). This finding is consistent with that described in the phase II study of the same regimen [5] and other studies [4]. However, the reason for incomplete suppression of spermatogenesis within and between populations is not yet understood. Incomplete gonadotrophin suppression due to variations of pharmacogenetics is one plausible explanation [17]. In the present study, higher baseline serum LH and serum LH and FSH during the suppression phase in partial suppressors were significant predictors of incomplete suppression of spermatogenesis. Furthermore, clinical features, such as total testis volume and BMI either alone or through interactions with circulating LH or FSH, were associated with incomplete spermatogenic suppression.

It has been reported that genetic polymorphism has an influence on pharmacological activity [18]. However, in the present study, DNA from the test group of partial suppressors and the control group of complete suppressors was analyzed to determine the polymorphisms of the CAG triplet repeat in AR gene and three different SNP in FSHR gene were found not to have any relationship to suppressor status.

Androgens exert their effects through AR, a DNA-binding transcription factor protein, encoded by a single-copy gene, and the polymorphic CAG triplet repeat is contained in exon 1 of AR gene. This polymorphism has been reported to influence sperm output most probably as a result of higher transactivational activity of AR [19], and a negative correlation has been reported between number of CAG triplet repeats and sperm concentration but not testicular size in normal men [20]. However, the

mean length of CAG triplet repeats in the two groups of this study was 22, consistent with previous research in the Chinese male population [21], without any significant difference between the test group of partial suppressors and the control group of complete suppressors. The present finding is also consistent with another study using androgen alone [22]**,** indicating that partial suppression of spermatogenesis is not directly related to polymorphism of AR gene in androgen alone studies. However, another *post-hoc* analysis of a mixed population treated with different regimens of hormonal male contraception has reported that azoospermia was more frequent in some treatments according to CAG triplet repeats [23]. In the present study, however, there was no significant relationship between the number of CAG triplet repeats and achievement of azoospermia, possibly due to lower power. Odds ratios (OR) obtained in the present study demonstrated that subjects with CAG triplet repeats numbering more than 22 had a chance of achieving azoospermia 1.5 times higher than that in cases with incomplete FSH suppression (> 0.2 IU/L). This reveals that the influence of polymorphism in AR gene on hormonal male contraception might be exerted when combined with other factors, such as suppression degree of serum gonadotrophins.

The key role for serum FSH in Sertoli cell and spermatogonial development has been established in all species. In monkeys, serum FSH levels are correlated with spermatogonial development and inadequate suppression of serum FSH is a potential reason for contraceptive failure [24]. FSH stimulates spermatogenesis using a specific receptor (FSHR) that is a member of the G protein-coupled receptor family. Mutation screening of the FSHR gene reveals various SNP, both in the core promoter and in the coding region. In particular, a common SNP in the core promoter of human FSHR gene at nucleotide position –29 has been reported. In exon 10, two SNP are also discovered at nucleotide position 919 and 2039 (numbered according to the translation start codon with ATG as "1") corresponding to amino acid positions 307 and 680 of the mature protein. Polymorphism within exon 10 results in two major, almost equally common allelic variants in the Caucasian population: Thr^{307}-Asn^{680} and Ala^{307}-Ser^{680} [25]. Investigations into the distribution of these two variants are controversial. The distribution of allelic variants was not different between normal and infertile men and women [26, 27], whereas significant difference was found between patients and controls [15, 28], suggesting that ethnic and gender differences could be involved and that the polymorphism might affect human reproductive function indirectly.

In the present study, the SNP at position –29 and in exon 10 in the two groups was analyzed. The prevalence of polymorphisms in this study was similar to that reported by others [29]. The haplotypes determined by the three SNPs of the FSHR gene were analyzed and restriction fragment length polymorphism analysis has confirmed complete linkage between the two allelic variants at positions 307 and 680. Considering the polymorphism in the promoter as well, four most common haplotypes result from the three SNPs of FSHR gene: A^{-29}-A^{919}-A^{2039} (A-Thr-Asn), G^{-29}-A^{919}-A^{2039} (G-Thr-Asn), A^{-29}-G^{919}-G^{2039} (A-Ala-Ser) and G^{-29}-G^{919}-G^{2039} (G-Ala-Ser) [14]. These four haplotypes accounted for 77.8% of FSHR alleles of the two groups, whereas in Caucasian population they account for over 99% [30], indicating an ethnic difference. Nevertheless, unlike in other research in women [31], in the present study, these polymorphisms did not determine likelihood of partial or complete suppression of spermatogenesis nor was there any relationship found between FSHR polymorphisms and basal FSH levels.

In conclusion, partial or incomplete suppression of spermatogenesis status induced by 500 mg TU monthly injections is attributable to both hormonal and clinical factors, whereas polymorphisms in AR and FSHR genes seem to have no direct influence. The relationship between genetic polymorphism and partial suppression of spermatogenesis requires more extensive testing with larger sample sizes.

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Edited by Dr Susan Benoff and Dr Ralf Henkel

Let's celebrate the 10th Anniversary of Asian Journal of Andrology

1992 *Asian Journal of Andrology (AJA) was conceived at the First Asian & Oceanic Congress of Andrology by the Executive Council of the Asian Society of Andrology to be its official publication.*
Prof Shao-Zhen QIAN was appointed the Editor-in-Chief

1998 *The Council delegated the production of AJA to the Shanghai Institute of Materia Medica, Chinese Academy of Sciences.*

1999 *The AJA was approved by the Chinese Government.*
An Advisory Board of international scientists and an Editorial Board and a Corresponding Editors Board of Asian scientists were formed.
The first issue, representing the outcome of their careful work, was produced.

2000 *AJA was indexed in SCI expanded and other important international Indexing systems.*

2002 *The first ISI Impact Factor, 0.827, was released by JCR.*
The First Asia-Pacific Forum on Andrology (FAPFA) was sucessfully held in Shanghai, China.

2003 *The ISI Impact Factor rose beyond one point and to 1.064.*

2005 *The four-year cooperation with Blackwell publishing group began.*

2006 *The journal was bimonthly published.*
The new Editor-in-Chief , Prof Yifei Wang was appointed .
The Second Asia-Pacific Forum on Andrology (2APFA) was held successfully in Shanghai, China.

2007 *The third-round Editorial Board was established.*
The Shanghai Jiaotong University became the co-sponsor of the journal.

2008 *The new cooperation relationship was established with Nature Publishing Group.*

2009 *The journal will celebrate its 10th Anniversary, on the occasion of the Third Asia-Pacific Forum on Andrology (3APFA) in October 10–13, Naning, Shanghai.*

We will review the past, summarize the present and shape the future!
Welcome you to be with us there!