

## 불임남성에서 방향화효소 억제제의 치료 효과

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### The Effectiveness of Aromatase Inhibitor in Infertile Male

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**Objective:** We investigated whether serum testosterone to estradiol ratio was decreased in infertile men and whether this condition can be corrected with oral aromatase inhibitor.

**Method:** The serum testosterone to estradiol ratio of 26 men with testicular failure were compared with those of normal semen analysis parameter, 89 control reference group. All of 26 testicular failure group were diagnosed with the previous testicular biopsy. Then 46 men with oligospermia and/or asthenospermia were selected and treated with 1 mg of the aromatase inhibitor anastrozole (Arimidex<sup>®</sup>) orally once daily for 3 months. Testosterone to estradiol ratio and semen analyses were evaluated during anastrozole therapy.

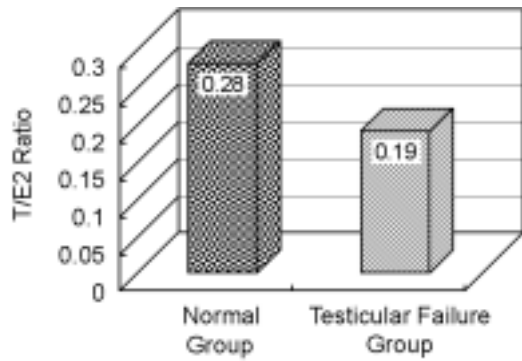
**Results:** The testosterone level of testicular failure group was significantly lower and the testosterone to estradiol ratio was more decreased than normal semen parameter group. Forty six on-anastrozole group had significantly lower testosterone (4.6 versus 5.7 ng/ml,  $p < 0.01$ ) and higher estradiol (15.9 versus 23.4 pg/ml,  $p < 0.01$ ) than pre-anastrozole group, resulting in a decreased testosterone to estradiol ratio ( $0.21 \pm 0.07$  versus  $0.39 \pm 0.15$ ,  $p < 0.01$ ). Semen analyses before and during anastrozole treatment revealed significant increases in sperm count (35.5 versus 52.2 million sperm per ml,  $p < 0.01$ ) and motility (22.9% versus 29.3%,  $p < 0.01$ ).

**Conclusions:** We identified infertile men with testicular failure had hormonal changes characterized by a decreased serum testosterone to estradiol ratio. The ratio can be corrected with aromatase inhibitor, resulting in a significant improvement in semen parameters.

**Key Words:** Infertility, Aromatase inhibitor, Testosterone, Estradiol

(testicular failure) 가 . 가  
10% 가 ,<sup>1</sup> 가 (estradiol) 가  
(testosterone) 가 .  
(follicular stimulating hormone) (nonobstructive azoosper-

mia) 가 가 ) 2 .  
 2-4 89 26  
 (Leydig cell) (androgens) (T/E2)  
 (peripheral aromatization)  
 , P-450 (cy- (oligospermia)  
 tochrome P-450) , (asthenospermia) 46 T/  
 , E2 .  
 20% .<sup>5</sup> anastrozole (Arimidex<sup>®</sup>, Astrazeneca, Swe-  
 (aromatase activity) , 가 den) 1 1 1 mg 3 . Ana-  
 (luteinizing hormone) ( strozole 3  
 , T/E2)  
 8 10  
 .<sup>6-8</sup> <sup>125</sup>I radioimmu-  
 (aromatase inhibitor) noassay DPC's Coat-A-Count Total Testosterone kit  
 (androstenedione) , intraas-  
 (estro- say interassay coefficient 17% 11% .  
 ne) .<sup>9</sup> ADALTIS' Estradiol Maia kit  
 (idiopathic oligo- intraas-  
 spermia) Biochem Immunosystems' FSH MAIAclone kit intraas- interassay  
 testolactone ADALTIS' LH MAIAclone kit coefficient 5.4% 3.5% ,  
 가 10-12 intraassay interassay coefficient 9.6%  
 .<sup>10-12</sup> 3.4% . Paired t test anastrozole  
 , p<0.01  
 가 .  
 .  
 4.8±2.1 ng/  
 ml, 3.5±0.8 ng/ml (p<0.01),  
 2002 6 2003 1 1 17.99±5.26 pg/ml, 19.7±5.7 pg/ml (p>0.05)  
 (J.T.S) T/E2 0.28±0.10, 0.19±0.05  
 , , , ( (p<0.01) (Figure 1).



**Figure 1.** Testosterone-to-estradiol ratios are higher in normal group than in testicular failure group ( $p < 0.01$ ).

**Table 1.** Testosterone, estradiol and testosterone-to-estradiol ratios before and during anastrozole treatment ( $p < 0.01$ )

	Testosterone (ng/ml)	Estradiol (pg/ml)	T/E2
Pre-anastrozole	$4.6 \pm 1.4$	$23.4 \pm 9.5$	$0.21 \pm 0.07$
On anastrozole	$5.7 \pm 1.6$	$15.9 \pm 4.9$	$0.39 \pm 0.15$

**Table 2.** Sperm count and motility before and during anastrozole treatment ( $p < 0.01$ )

	Sperm count ( $\times 10^6$ )	Motility (%)
Pre-anastrozole	$35.5 \pm 36.6$	$22.9 \pm 15.3$
On anastrozole	$52.2 \pm 42.1$	$29.3 \pm 20.1$

46 anastrozole, T/E2  
 $4.6 \pm 1.4$  ng/ml  $5.7 \pm 1.6$  ng/ml,  $23.4 \pm 9.5$  pg/ml  
 $15.9 \pm 4.9$  pg/ml,  $0.21 \pm 0.07$   $0.39 \pm 0.15$   
 가 ( $p < 0.01$ )

(Table 1).

( $35.5 \pm 36.6$  vs.  $52.2 \pm 42.1$ ,  $p < 0.01$ )

( $22.9 \pm 15.3$  vs.  $29.3 \pm 20.1$ ,  $p < 0.01$ )

(Table 2). Anastrozole

P450  
 (specific cytochrome P450 aromatase) NADPH  
 P450 (NADPH-cytochrome P450  
 reductase)

(microsomal enzymatic complex)

P450

가 <sup>16</sup> (in vitro study)

<sup>6,16,17</sup>

30~50%

<sup>1</sup>

<sup>18</sup>

1995  
 tamoxifen

FDA

<sup>19,20</sup>

Turner

anastrozole

ana-

(estrogen receptor)

가 (fertility)

<sup>13-15</sup>

가 knockout

가

가

가

Akiyama .<sup>21</sup>  
 가가 .<sup>22</sup> anastrozole  
 가  
 가  
 Turner anastro-  
 zole 가  
 가  
 가 (fertility) 가  
 가  
 가 .<sup>1</sup> 가  
 가 T/E2 가  
 . Pavlovich  
 T/E2 가  
 (eja-  
 culatory sperm) 가  
 가 .<sup>23</sup>  
 anastrozole  
 가,  
 E2 가가 T/  
 가  
 가  
 .  
 tone  
 anastrozole

of testicular function in rats by estriol and proge-  
 sterone. *J Steroid Biochem* 1978; 9: 1257-9.

3. Jones TM, Fang VS, Landau RL, Rosenfield R. Direct inhibition of Leydig cell function by estradiol. *J Clin Endocrinol Metab* 1978; 47: 1368-73.
4. Kalla NR, Nisula BC, Menard R, Loriaux DL. The effect of estradiol on testicular testosterone biosynthesis. *Endocrinology* 1980; 106: 35-9.
5. de Jong FH, Hey AH, van der Molen HJ. Effect of gonadotrophins on the secretion of estradiol 17-β and testosterone by the rat testis. *Endocrinology* 1973; 57: 277-84.
6. Inkster S, Yue W, Brodie A. Human testicular aromatase: immunocytochemical and biochemical studies. *J Clin Endocrinol Metab* 1995; 80: 1941-7.
7. Kulin HE, Reiter EO. Gonadotropin suppression by low dose estrogen in men: evidence for differential effects upon FSH and LH. *J Clin Endocrinol Metab* 1972; 35: 836-9.
8. Veldhuis JD, Sowers JR, Rogol AD, Klein FA, Miller N, Dufau ML. Pathophysiology of male hypogonadism associated with endogenous hyperestrogenism. Evidence for dual defects in the gonadal axis. *N Engl J Med* 1985; 312: 1371-5.
9. Brodie AM, Njar VC. Aromatase inhibitors and breast cancer. *Semin Oncol Suppl* 1996; 23: 10-20.
10. Vigersky RA, Glass AR. Effects of delta 1-testolactone on the pituitary-testicular axis in oligospermic men. *J Clin Endocrinol Metab* 1981; 52: 897-90.
11. Schill WB, Reiter F, Korting HC, Schwikert HU. Long-term therapy of oligozoospermia with the aromatase inhibitor testolactone. *Hautarzt* 1987; 38: 395-9.
12. Itoh N, Kumamoto Y, Maruta H, Tsukamoto T, Takagi Y, Mikuma N, et al. Therapeutic efficacy of testolactone (aromatase inhibitor) to oligozoospermia with high estradiol/testosterone ratio. *Nippon Hinyokika Gakkai Zasshi* 1991; 82: 204-9.
13. Korach KS, Couse JF, Curtis SW, Washburn TF, Lindzey J, Kimbro KS, et al. Estrogen receptor gene disruption: molecular characterization and ex-

1. Schlegel PN. How to do a workup for male infertility. *Med Aspects Hum Sex* 1991; 25: 28-32.
2. Ciaccio LA, Joseph AA, Kincl FA. Direct inhibition

- perimental and clinical phenotypes. *Recent Prog Horm Res* 1996; 51: 159-86.
14. Hess RA, Bunick D, Lee KH, Bahr J, Taylor JA, Korach KS, et al. A role for oestrogens in the male reproductive system. *Nature* 1997; 390: 509-11.
  15. Luconi M, Forti F, Baldi E. Genomic and nongenomic effects of estrogens: molecular mechanism of action and clinical implications for male reproduction. *J Steroid Biochem Mol Biol* 2002; 80: 369-81.
  16. Carreau S. Paracrine control of human Leydig cell and Sertoli cell function. *Folia histochem Cytobiol* 1996; 34: 111-9.
  17. Lambard L, Galeraud-Denis I, Bouraima H, Bourguiba S, Chocat A, Carreau S. Expression of aromatase in human ejaculated spermatozoa: a putative marker of mortality. *Mol Hum Reprod* 2003; 9: 117-24.
  18. Brodie AM. Aromatase inhibition and its pharmacologic implications. *Biochem Pharmacol* 1985; 34: 3213-9.
  19. Plourde PV, Yetes RA, Dyroff M, et al. The effect of Arimidex, a new potent aromatase inhibitor, on circulating estrogens in post-menopausal women. Presented at meeting of American Society of Clinical Oncology, Orlando, Florida, 1993 May; 16-8.
  20. Geisler J, King N, Dowsett M, Ottestad L, Lundgren S, Walton P, et al. Influence of anastrozole (Arimidex), a selective, nonsteroidal aromatase inhibitor on in vivo aromatisation and plasma oestrogen levels in post-menopausal women with breast cancer. *Br J Cancer* 1996; 74: 1286-91.
  21. Turner KJ, Morley M, Atanassova N, Swanston ID, Sharpe RM. Effect of chronic administration of an aromatase inhibitor to adult male rats on pituitary and testicular function and fertility. *J Endocrinol* 2000; 164: 225-38.
  22. Akiyama H. A study on testicular aromatase activity-spermatogenic damage in high testicular E2 models of rat. *Nippon Hinyokika Gakkai Zasshi* 1997; 88: 649-57.
  23. Pavlovich CP, King P, Goldstein M, Schlegel PN. Evidence of a treatable endocrinopathy in infertile men. *J Urol* 2001; 165: 837-41.
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