Clinical report about the effectiveness of andriol, tamoxifen, vitamin A and lecithin on low acrosome
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RESEARCH
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ABSTRACT
Background
Acrosin is the most important proteolytic enzyme in fertilization. Acrosin is usually present as an inactive acrosin zymogen. As the spermatozoon enters the zona pellucida of the egg, acrosin zymogen is activated; allowing the spermatozoon to go through the zona pellucida and bind to the egg.1 Acrosome dysfunction will affect fertilization, thus causing infertility. Nowadays in vitro fertilization and embryo transfer (IVF-ET) or intracytoplasmic sperm injection and embryo transfer (ICSI-ET) commonly used in patients with low acrosome function,2 4 and there has been (37.62±11.07)μIU/10⁶ sperm before treatment and raised to (52.68±15.68)μIU/10⁶ sperm after treatment and showed statistical difference (t=8.18, P=0.00). In all the 78 males, the acrosin of seven men (11 per cent) bellowed after treatment while the acrosin of 71 males (91 per cent) raised and ten couples (13 per cent) got pregnant.

Conclusion
The combined treatment of andriol, tamoxifen, vitamin A and lecithin were effective on low acrosin.

Key Words
Acrosin, spermatozoa, testosterone, tamoxifen, infertility

What this study adds:
1. What is known about this subject? There is a new way to improve acrosome function.

2. What new information is offered in this study? Tamoxifen with andriol maybe the better way to improve the acrosome function.

3. What are the implications for research, policy, or practice? The drugs could increase FSH concentration in the serum, indicating that acrosome function improving through the increasing of FSH.

Background
Acrosin is the most important proteolytic enzyme in fertilization. Acrosin is usually present as an inactive acrosin zymogen. As the spermatozoon enters the zona pellucida of the egg, acrosin zymogen is activated; allowing the spermatozoon to go through the zona pellucida and bind to the egg.1 Acrosome dysfunction will affect fertilization, thus causing infertility. Nowadays in vitro fertilization and embryo transfer (IVF-ET) or intracytoplasmic sperm injection and embryo transfer (ICSI-ET) commonly used in patients with low acrosome function,2 4 and there has been...
Clinical data
Seventy-eight male patients in the Reproductive Medicine Center from May 2013 to May 2015 were enrolled. These patients were aged between 23–49 years old and with 2–4 years of infertility, among which 1 were secondary infertility. Selection criteria: seminal volume ≥1.5ml, sperm concentration ≥1 x 10⁶/ml. Acrosin assayed below the normal range (normal range: 48.2–218.7μIU/10⁶ sperm).

The contribution of this report is that after using drug combination therapy, patients’ acrosin function was significantly improved. Before treatment, acrosin was (33.7±9.1)μIU/10⁶ sperm, with 2 patients’ acrosin ≤20μIU/10⁶ sperm (2.6 per cent), 15 patients’ acrosin between 20 <acrosin ≤30μIU/10⁶ sperm (19.2 per cent), 21 patients’ acrosin between 30 <acrosin ≤40μIU/10⁶ sperm (26.9 per cent), and 40 patients’ acrosin between 40 <acrosin ≤48.2μIU/10⁶ sperm (51.3 per cent, Table 1). Acrosin raised to (50±17.3)μIU/10⁶ sperm after treatment, and showed a significant difference between before and after treatment (t=7.86, P=0.00, Tables 1 and 2). Of all 78 patients, 7 patients (9 per cent) had decreased acrosin, 71 patients’ (91 per cent) increased, 18 patients’ (23 per cent) did not reach the normal range.

Discussion
The effect of this study is that after using drug combination therapy, patients’ acrosin function was significantly improved. Before treatment, acrosin was (33.7±9.1)μIU/10⁶ sperm. After treatment, acrosin raised to (48.84±12.97)μIU/10⁶ sperm, displayed a significant difference between before and after treatment (t=7.86, P=0.00). Of all 78 patients, 71 patients’ acrosin (91 per cent) increased, among which 18 patients’ acrosin (23 per cent) raised but did not reach the normal range; 7 patients (9 per cent) had decreased acrosin.

Concerning the therapeutic time, the proportion of patients improved for one month is the most, accounting for 37.8 per cent of the total patients; therapeutic time of two
months occupied 19.5 per cent and three months took up 15.9 per cent, presenting an overall decreasing trend, which indicated the effectiveness of treatment from the side. Besides, it also suggested that the main cause of infertility in these couples may result from the man. As the quality of semen was improved, the patient’s conception rate increased the number and time of visits decreased. For the patients whose treatment time was over four months, infertility factors might also exist in his wife, leading to longer treatment time.

Second, experimental results demonstrated that compared to the values before treatment, the sperm concentration \((t=3.59, P=0.001)\) increased, while seminal volume \((t=1.93, P=0.057)\), normal morphology \((t=0.64, P=0.0527)\) and progressive sperm \((t=1.42, P=0.166)\) did not show statistical significance after treatment, which was consistent with previous studies.\(^6-14\)

Third, considering the treatment outcome, after treatment, among all the 78 patients, 10 couples (13 per cent) naturally conceived and 2 (3 per cent) aborted. 22 patients switched to ART to help pregnancy for various reasons and others were left to follow up. Because they were all outpatients, follow-up survey was not perfect. The curative effects were obtained completely based on patients’ subsequent visits. Presumably the actual pregnancy rate should be higher than the current statistics.

Fourth, this treatment regimen adopted tamoxifen-testosterone-vitamin A-lecithin combination therapy.

The acrosome is a vital tool for the combination of sperm and egg. However, there has been not much research on acrosin and less reports on the treatment of acrosomal dysfunction. In 1997, Adamopoulos et al. described andriol-tamoxifen combined treatment of oligo (weak) sperm disease, and the data suggested that the treatment group could improve the function of the acrosome.\(^6\) In 2013 Hongyu PENG et al. reported the effect of clomiphene on acrosin, the acrosin raised to \((59.2\pm28.3)\muIU/10^6\) sperm in clomiphene treatment group while the acrosin was \((36.2\pm16.9)\muIU/10^6\) sperm in the control group, and there was statistically significant difference between these two groups.\(^7\) It was supposed that the drug might play the role by regulating the sex hormones or mediating the calcium influx. Clomiphene might alter the synthesis and secretion of estrogen and androgen, thus affecting sperm acrosin activity. Jiahui et al. revealed that clomiphene could increase calcium influx,\(^8\) whereas acrosin activation required calcium influx,\(^9\) suggesting that clomiphene may improve acrosin activity by increasing cellular calcium concentration.\(^7\) Tamoxifen had similar effectiveness and mechanism with clomiphene.

The reason for adding andriol lay in the fact that tamoxifen alone improved the quality of semen, but the conception rate were not changed much, presumably due to no increase in progressive sperm.\(^6\) Adding androgenic drugs could improve epididymis function, raising patients’ conception rate.\(^6,10,11\) The reason for adding vitamin A was that lack of vitamin A was one of the causes of preventing spermatogenesis.\(^12\) Basic research showed that vitamin A was converted to the active product retinol in the body, which in turn induced spermatogonium differentiation and meiosis.\(^13,14\)

In this report, some patients’ proportion with abnormal hypo-osmotic swelling test (HOST) was quite high. Among 78 patients, 30 (38 per cent) had a decrease in HOST \((44.08\pm9.29)\) per cent. Nowadays there has been no report on treatment for HOST reduce. During clinical practice, we use lecithin and phosphatidylcholine to treat HOST reduce, which has an obvious effect. However, considering the higher cost of phosphatidylcholine, currently the main drugs for HOST reduce is lecithin, and the effect is satisfying. Given that in abnormal acrosin patients, the incidence of HOST abnormalities was relatively high, the treatment regimen of acrosin dysfunction added lecithin. The therapeutic effect demonstrated that after 1–2 months treatment, HOST could reach the normal range. Relevant literatures, basic research and in vitro experiments all suggested that lecithin promoted acrosome reaction.\(^15\)

This study did not analyze hormone levels. From Adamopoulos\(^16\) and our previous reports,\(^17\) the use of tamoxifen-andriol could increase FSH concentrations in the serum, indicating that this regimen might affect spermatogenesis by altering hormone levels.\(^10\) As for whether the drug improves acrosome function through the calcium channel, further study is still needed.

Compared with the reports of Adamopoulos et al.\(^6\) or PENG et al.,\(^7\) drug combination showed more better results, some couples (13 per cent) got pregnancy. It showed that drug combination maybe got better effectiveness than drug single.

Fifth, the treatment cycle displayed that among 78 patients, 71 (91 per cent) had acrosin improvement after one month treatment; but the peak of acrosome improvement appeared in 2–3 months; in the 4th month of medication,
the change of the patient’s acrosin activity entered the platform stage and no significant change had appeared, whose reason was not clear. It was presumed that it might be caused by the drug bioavailability’s saturation after long-term medication.

Conclusion
The acrosome plays a major role in sperm-egg binding, and the lack of acrosome function can cause male fertility disorders. The combination regimen of andriol, tamoxifen, vitamin A and lecithin can effectively improve the acrosome function, and treat male infertility caused by the lack of sperm count and acrosome dysfunction.

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PEER REVIEW
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CONFLICTS OF INTEREST
The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL
The ethics committee of Peking University Shenzhen Hospital had approved this study, the ethic reference number is 201302044.
### Table 1: The difference of acrosome

| Acrosin (μIU/10⁶ sperm) | Number of patients | Percentage |
|------------------------|--------------------|------------|
| acrosin≤20             | 2                  | 2.6%       |
| 20<acrosin≤30          | 15                 | 19.2%      |
| 30<acrosin≤40          | 21                 | 26.9%      |
| 40<acrosin<48.2        | 40                 | 51.3%      |
| Total                  | 78                 | 100.0%     |

### Table 2: Comparison of seminal parameters before and after treatment

|                     | Volume (ml) | Concentration (×10⁶/ml) | Progressive (%) | Acrosome (μIU/10⁶ sperm) | Normal (morphology %) |
|---------------------|-------------|-------------------------|-----------------|--------------------------|-----------------------|
| **Before treatment**|             |                         |                 |                          |                       |
|                     | 3.77±1.57   | 33.43±19.77             | 31.23±14.75     | 37.62±111.06             | 2.23±1.53             |
| **After treatment** |             |                         |                 |                          |                       |
|                     | 4.00±1.56   | 48.79±27.42             | 35.92±15.77     | 52.68±15.67              | 2.19±1.70             |
| T                   | -1.93       | -5.05                   | -2.14           | -8.18                    | 0.24                  |
| P                   | 0.057       | 0.000                   | 0.036           | 0.000                    | 0.811                 |