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Original Article

Prodom: a new assisted reproductive device to treat male infertility caused by impaired semen liquefaction

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Abstract: Impaired semen liquefaction (ISL) is one of the most common causes of male infertility. Western and Chinese medicines are primary methods for the treatment of ISL. The present research team previously used an *in vitro* injection method and developed a new auxiliary reproductive device, prodom, to treat ISL. The aim was to evaluate the clinical efficacy of prodom, which assists in the administration of chymotrypsin to the spouse's vagina in ISL patients. The patients were divided into the prodom-assisted chymotrypsin treatment (PACT) group (n = 109), syringe-assisted chymotrypsin treatment (SACT) group (n = 84), and traditional treatment (TT) group (n = 81), randomly in the first stage. When the first stage of treatment failed, the patients were regrouped and classified as the second stage. Pregnancy rate, time to conception, and treatment costs were compared for each group. In the first stage, for the PACT group, SACT group, and TT group, the pregnancy rate was 53.21%, 47.62%, and 24.69%, respectively. Time to conception was 4.57±2.04 months, 4.85±1.87 months, and 5.75±1.86 months, respectively. Treatment cost was $ 1,723±721, $ 1,343±268, and $ 2,919±892, respectively. Differences were significant ($P < 0.05$). In the second stage, compared with the group using artificial insemination with the husband's semen, differences in time to conception and treatment costs for PACT, SACT, and TT groups were significant ($P < 0.001$). In conclusion, prodom can effectively assist chymotrypsin in the treatment of male infertility caused by ISL.

Keywords: Impaired semen liquefaction, male infertility, assisted reproductive technology, prodom, chymotrypsin

Introduction

Impaired semen liquefaction (ISL) means that the time of semen liquefaction after ejaculation is more than one hour [1]. This condition is one of the most common causes of male infertility, with approximately 2.51%-42.65% of male infertility caused by ISL [2-6]. Prostate disease is the leading cause of ISL [2-6]. At present, the pathogenesis of ISL is unclear. It is generally believed that semen liquefaction and solidification are influenced by semenogelin, primarily found in the seminal vesicles, and by liquefaction factor, found in the prostate [6-10]. One known cause of ISL is decreased activity of enzymes during reduced prostatic secretion. Decreased protease secretion is particularly important because proteases hydrolyze proteins during the semen liquefaction process to indicate prostate enzyme (s) known to hydrolyze semen [2, 8, 11, 12]. Further causes of ISL include increased levels of semenogelin, which disturb the balance of liquefaction and solidification factors. In addition, seminal vesiculitis, a lack of trace elements (magnesium and zinc), and congenital deficiencies of the prostate can cause poor semen liquefaction [2, 13-18]. Western and Chinese medicines are the primary methods used to treat ISL [2, 18, 19].

However, because of the complex metabolic mechanisms of the human body, neither oral Western medicine nor Chinese medicine can completely improve ISL through *in vivo* approaches [18-30]. Therefore, to achieve a more ideal therapeutic effect, the focus of treatment has shifted to improving ISL through *in vitro* approaches. To treat male infertility caused by ISL, the present team once used a syringe to assist the injection of chymotrypsin into the vagina of the spouse when couples have sex. This treatment achieved a certain effect. However, there are still some defects in the syringe injection process. For example, it does not ensure that chymotrypsin is fully exposed to semen. It can cause a partial loss of semen

from the vagina and can be inconvenient to operate, cause paining for the spouse. These issues make some patients and spouses unwilling to receive the treatment. Therefore, the present team explored a better *in vitro* injection method and developed a new auxiliary reproductive device [31]. The device was named "prodom". Prodom is a device that is worn on the penis. Through this device, insufficient or abnormal components of semen can be supplemented. Prodom has the certain advantages. When the husband and wife have sex, the prodom injection is synchronized with ejaculation. It can ensure that semen fully contacts with chymotrypsin. It prevents semen leakage from the vagina and it can achieve the goal of restoring fertility while preserving the pleasures of sexual life for males with infertility.

At present, prodom has entered the clinical trial stage. Its clinical efficacy has been preliminarily evaluated. Therefore, the present study was carried out to evaluate its clinical effects for male infertility caused by ISL.

Patients and methods

Patients

The current study was a randomized controlled trial study. A consecutive series of data, covering 337 ISL patients, during the period of January 2012 to May 2018, was collected from Affiliated Hospital of Zunyi Medical University in China. Inclusion criteria were: clinical records of all ISL patients (outpatient during January 1, 2012 to May 31, 2018) should be complete and accurate, with follow-up visits lasting for 0.75-6 years. Exclusion criteria were: (1) Nonimpaired semen liquefaction; (2) Organic diseases, including uremia, cirrhosis and liver failure, lung failure, endocrine dysfunction, mental disorder, azoospermia, or severe oligospermia; (3) Incomplete clinical records; or (4) Willing termination of the treatment or refusal of follow-up visits. A total of 63 patients gave up treatment halfway, but the remaining 274 completed the study. The Institutional Review Board of the Affiliated Hospital of Zunyi Medical University approved the present study in January 2018.

Experimental group and intervention measures of each group

A total of 63 patients that gave up treatment halfway were excluded. The remaining 274 patients with ISL were divided into three groups, the prodom-assisted chymotrypsin treatment (PACT) group (n = 109), syringe-assisted chymotrypsin treatment (SACT) group (n = 84), and traditional treatment (TT) group (n = 81), according to the different treatment methods. All patients were divided into groups using a completely randomized method. Each subject was numbered according to the order of seeing a doctor and received a random number using the random number table. The random number was divided by 3. The resulting remainder of 0, 1, and 2 corresponded to the PACT group, SACT group, and TT group, respectively. Envelope concealment was used to randomize distribution schemes. The PACT group had chymotrypsin 4000 IU (1 mL) injected into the vagina of the spouse through the prodom during intercourse and synchronously with ejaculation. This helped to mix the chymotrypsin with semen. In the SACT group, chymotrypsin 2000 IU (0.5 mL) was injected into the vagina of the spouse through a 5-mL ordinary syringe before the penis was inserted and after the penis was removed during intercourse. The TT group used 1,000 mg of vitamin C and 100 mg of vitamin E, which were administered every day, along with 10 mL of zinc gluconate and a spermatogenic tablet (Traditional Chinese medicine), administered 3 times a day as supplements.

Operation steps for the use of prodom assisted chymotrypsin

Open the syringe wrapper→obtain syringe and its needles→chymotrypsin prepared in the syringe→open the prodom wrapper and obtain prodom→tear off the inner wall paper and paste the prodom on the penis head back and out of the penis head→remove the outer wall paper of the prodom→the syringe with chymotrypsin prepared in advance was connected to the drug injection catheter connector of the prodom→sexual intercourse→during ejaculation, one of the couple injects the chymotrypsin in the syringe into the vagina→continue to thrust the penis 2 to 3 times for chymotrypsin to mix with semen→draw the penis out of the vagina→tear off the prodom attached to the penis→end of operation.

Operation steps for the use of syringe assisted chymotrypsin

Open the syringe wrapper→obtain syringe and its needles→chymotrypsin was prepared in the syringe→the chymotrypsin prepared in the syringe was injected into the spousal vagina by

the husband (for the first time)→sexual intercourse→after ejaculation, draw the penis out of the vagina→chymotrypsin prepared in the syringe was injected into the spousal vagina by husband (for the second time)→reinsert the penis into the vagina and thrust the penis 2 to 3 times for chymotrypsin to mix with semen→draw the penis out of the vagina→end of operation.

Clinical data extraction

Available data included semen parameters (semen volume, pH, liquefaction time, sperm density, sperm motility, live sperm rate, and sperm morphology), duration of infertility, routine urine test (urine leukocytes and urine red blood cells), prostatic enlargement, seminal vesicle enlargement, white blood cells in prostatic massage fluid, presence or absence of chronic prostatitis, history of chronic prostatitis, history of seminal vesiculitis, patient age and spouse (female) age, pregnancy, time to conception, and treatment costs. Subjects were evaluated according to the different treatment methods. They were divided into the PACT group, SACT group, and TT group in the first stage. When the first stage of treatment failed, the treatment methods were replaced with other treatment methods. The patients were also grouped according to their treatment method and classified as the second stage.

Diagnosis standards

ISL refers to liquefaction time that exceeds 60 minutes. Male infertility refers to failure to conceive with couples living together for more than one year, without any contraceptive measures, not caused by female infertility. ISL and male infertility were diagnosed using the Fifth Edition Standards in 2010 *WHO laboratory test manual for human semen and sperm-cervical mucus interactions* [1].

Follow-up

The median follow-up time was 3.5 (range 0.75-6) years. All patients were followed up via telephone and regular outpatient visits. Follow-up items through telephone consultations included health status, pregnancy status, and time of conception. Outpatient follow-ups included general physical examinations, routine blood and blood biochemical examinations, and semen quality analysis.

Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, USA) version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Selected characteristics (including clinical data parameters described above that were collected) were compared between treatment group cases using the Chi-squared test for categorical variables and *t*-test and variance analysis for quantitative data. Numerical variables are presented as mean ± standard deviation and categorical variables are presented as percentages. Multivariate logistic regression analyses, adjusted for potential confounders (age), were performed to assess the association of pregnancy and time to conception with different treatments. Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were simultaneously estimated by logistic regression analyses. Differences are significant when $P < 0.05$.

Results

Baseline characteristics of ISL patients in the PACT group, SACT group, and TT group

Excluding the 63 patients that halted treatment halfway, 274 patients had semen liquefaction times of more than 60 minutes. The time since infertility diagnosis ranged from 1 to 20 years, while the duration time of infertility was 4.64±2.52 years. Patient ages ranged from 21 to 48, with an average age of 31. Spouse (female) ages ranged from 21 to 39, with an average age of 28. According to different treatment methods, 274 patients were divided into the PACT group (n = 109), SACT group (n = 84), and TT group (n = 81). As shown in **Table 1**, available data included semen parameters (semen volume, pH, liquefaction time, sperm density, sperm motility, live sperm rate, and sperm morphology), duration time of infertility, routine urine test (including urine leukocytes and urine red blood cells), prostatic enlargement, seminal vesicle enlargement, white blood cells in prostatic massage fluid, presence or absence of chronic prostatitis, history of chronic prostatitis, history of seminal vesiculitis, patient age, and spouse (female) age. There were no significant differences between the three groups (all $P>0.05$).

Table 1. Baseline characteristics of clinical data in each group

Parameters \ Group	PACT group (n = 109)	SACT group (n = 84)	TT group (n = 81)	*P* value
Patient (Male) Age (Year)	30.44±6.55	31.90±6.42	30.05±5.57	0.126†
Spouse (female) Age (Year)	27.28±4.94	28.52±4.64	27.31±4.57	0.143†
Semen parameters				
Semen volume (ml)	3.46±0.91	3.43±0.84	3.51±0.77	0.809†
pH	7.41±0.16	7.44±0.17	7.40±0.15	0.159†
Liquefaction time (Min)	>60	>60	>60	NS
Sperm density ($\times 10^6$/ml)	46.53±11.16	45.00±9.11	45.49±9.23	0.552†
Sperm motility, %				
a Class	19.09±3.39	19.18±3.69	18.57±3.16	0.457*
a+b Class	42.70±5.72	42.20±4.95	42.85±5.66	0.732*
Live sperm rate, %	56.52±8.89	55.76±8.97	55.37±8.98	0.662*
Sperm morphology, %				
Normal	29.70±7.32	29.71±7.52	30.05±6.99	0.938*
Abnormal	70.30±7.32	70.29±7.52	69.95±6.99	0.938*
Duration time of infertility (Year)	4.67±3.58	4.79±2.93	4.46±2.64	0.789*
Routine urine test				
WBC, %				0.844*
(+)	5.5 (6/109)	7.1 (6/84)	7.4 (6/81)	
(-)	94.5 (103/109)	78/92.9	92.6 (75/81)	
RBC, %				0.928*
(+)	6.4 (7/109)	6.0 (5/84)	7.4 (6/81)	
(-)	93.6 (102/109)	94.0 (79/84)	92.6 (75/81)	
Prostatic enlargement, %				0.876*
Yes	9.2 (10/109)	7.1 (6/84)	8.6 (7/81)	
No	90.8 (99/109)	92.9 (78/84)	91.4 (74/81)	
Seminal vesicle enlargement, %				0.439*
Yes	4.6 (5/109)	4.8 (4/84)	8.6 (7/81)	
No	95.4 (104/109)	95.2 (80/84)	91.4 (74/81)	
Prostatic massage fluid, %				0.924*
WBC (+)	7.3 (8/109)	7.1 (6/84)	8.6 (7/81)	
WBC (-)	92.7 (101/109)	92.9 (78/84)	91.4 (74/81)	
Chronic prostatitis, %				0.382*
Yes	12.8 (14/109)	7.1 (6/84)	8.6 (7/81)	
No	87.2 (95/109)	92.9 (78/84)	91.4 (74/81)	
History of chronic prostatitis, %				0.544*
Yes	4.6 (5/109)	8.3 (7/84)	7.4 (6/81)	
No	95.4 (104/109)	91.4 (77/84)	92.6 (75/81)	
History of seminal vesiculitis, %				0.895*
Yes	3.7 (4/109)	4.8 (4/84)	4.9 (4/81)	
No	96.3 (105/109)	95.2 (80/84)	95.1 (77/81)	
Give up treatment, %	12.80 (16/125)	29.41 (35/119)	12.90 (12/93)	**0.002***

Abbreviations: PACT, prodom-assisted chymotrypsin treatment; SACT, syringe-assisted chymotrypsin treatment; TT, traditional treatment. *P*-values were calculated using † one-way analysis of variance (one-way ANOVA), *Chi-squared; The boldface represents statistical significance.

Of the 63 patients that gave up treatment, the PACT group accounted for 12.80% (16/125), the SACT group for 29.41% (35/119), and the TT group for 12.90% (12/93). Moreover, the

Table 2. Pregnancy rate/time to conception/treatment cost between groups were compared in the first stage

Parameters \ Group	PACT group (n = 109)	SACT group (n = 84)	TT group (n = 81)	Total (n = 274)	*F*	*P* value
Pregnancy rate, %	53.21 (58/109)	47.62 (40/84)	24.69 (20/81)	43.07 (118/274)	8.648	< 0.001
Time to conception (months)	4.09±2.04	4.85±1.87	5.75±1.86	4.86±1.99	2.631	0.024
Treatment cost ($)	1,723±721	1,343±268	2,919±892	1,797±833	40.763	< 0.001

Abbreviations: PACT, prodom-assisted chymotrypsin treatment; SACT, syringe-assisted chymotrypsin treatment; TT, traditional treatment. *P*-values were calculated using one-way analysis of variance (one-way ANOVA). There were statistically significant differences in the pregnancy rate, time to conception, and treatment costs between groups (*P* < 0.001, = 0.024, < 0.001, respectively). Paired comparisons found that the pregnancy rate was the highest and the time to conception was the shortest in PACT group. The pregnancy rate was the was the shortest and the time to conception was the longest in TT group, while the SACT group exhibited intermediate results. Differences were statistically significant (all *P* < 0.05) between the three groups - PACT vs SACT, PACT vs TT, and SACT vs TT. Treatment cost was the highest in the TT group. It was minimal in the SACT group, while the PACT group exhibited intermediate results. There were statistical significances between the TT group vs the PACT group and between the TT group vs the SACT group (both with *P* < 0.05), but there was no statistical significance between the PACT group vs the SACT group (*P*>0.05).

rate of abandoning treatment in the PACT group was lower than that in the other two groups. Differences were statistically significant (*P* = 0.002).

Pregnancy rate, time to conception, and treatment costs in the PACT group, SACT group, and TT group compared in the first stage

As shown in **Table 2**, in the PACT group, SACT group, and TT group, the pregnancy rate was 53.21% (58/109), 47.62% (40/84), and 24.69% (20/81), respectively. Time to conception was 4.09±2.04 months, 4.85±1.87 months, and 5.75±1.86 months, respectively. Treatment cost was $ 1,723±721, $ 1,343±268, and $ 2,919±892, respectively. There were significant differences in pregnancy rates, time to conception, and treatment costs between groups (*P* < 0.001, = 0.024, < 0.001, respectively). Paired comparisons found that pregnancy rates were the highest and the time to conception was the shortest in PACT group. Pregnancy rates were the shortest and the time to conception was the longest in TT group, while the SACT group exhibited intermediate results. Differences were statistically significant (all *P* < 0.05) between the three groups - PACT vs SACT, PACT vs TT, and SACT vs TT. Treatment cost was the highest in the TT group. It was minimal in the SACT group, while the PACT group exhibited intermediate results. There were statistically significant differences between the TT group and PACT group and between the TT group and SACT group (both with *P* < 0.05), but there was no statistical significance between the PACT group and SACT group (*P*>0.05).

Pregnancy rate, time to conception, and treatments cost between groups compared in the second stage treatment

After 9 months, unfertilized patients in the first stage of treatment in the prodom- assisted chymotrypsin treatment group (n = 51), SACT group (n = 44), and TT group (n = 61) were divided into the second stage for treatment by other methods. The pregnancy rate was 33.33% (4/12), time to conception was 11±1.83 months, and treatment cost was $ 1,637±79 in the PACT group that was changed to the TT group. The pregnancy rate was 50% (14/28), time to conception was 11.36±1.78 months, and treatment cost was $ 2,684±187 in the PACT group combined with the TT group. The pregnancy rate was 63.64% (7/11), time to conception was 33.43±5.38 months, and treatment cost was $ 17,920±6,214 in the PACT group that was changed to artificial insemination with husband's semen (AIH) group. The pregnancy rate was 33.33% (4/12), time to conception was 12±1.63 months, and treatment cost was $ 1,637±153 in the SACT group that was changed to the TT group. The pregnancy rate was 50% (9/18), time to conception was 13.67± 2.35 months, and treatment cost was $ 4,045±738 in the SACT group combined with the TT group. The pregnancy rate was 42.86% (6/14), time to conception was 29.5±7.79 months, and treatment cost was $ 18,080± 4,877 in the SACT group that was changed to the AIH group. The pregnancy rate was 72.41% (21/29), time to conception was 8.62±2.58 months, and treatment cost was $ 2,451±196 in the TT group that was changed to the PACT

Table 3. Pregnancy rate/time to conception/treatment cost between groups were compared in the second stage.

Parameters \ Group	PACT was changed to TT group (n = 12)	PACT combined with TT group (n = 28)	PACT was changed to AIH (n = 11)	SACT was changed to TT group (n = 12)	SACT combined with TT group (n = 18)	SACT was changed to AIH (n = 14)	TT was changed to PACT group (n = 29)	TT was changed to SACT group (n = 20)	TT was changed to AIH (n = 12)	Total (n = 156)	*F*	*P* value
Pregnancy rate (%)	33.33 (4/12)	50 (14/28)	63.64 (7/11)	33.33 (4/12)	50 (9/18)	42.86 (6/14)	72.41 (21/29)	70 (14/20)	66.67 (8/12)	55.77 (87/156)	1.561	0.141
Time to conception (months)	11±1.83	11.36±1.78	33.43±5.38	12±1.63	13.67±2.35	29.5±7.79	8.62±2.58	9.43±2.28	35.75±8.08	16.02±10.59	69.84	< 0.001
Treatment cost ($)	1,637±79	2,684±187	17,920±6,124	1,637±153	4,045±738	18,080±4,877	2,451±196	2,339±250	21,747±3,533	6,657±7,666	101.121	< 0.001

Abbreviations: PACT, prodom-assisted chymotrypsin treatment; SACT, syringe-assisted chymotrypsin treatment; TT, traditional treatment; AIH, artificial insemination with husband's semen. *P*-values were calculated using one-way analysis of variance (one-way ANOVA). There was no significant difference ($P = 0.141$) in the pregnancy rate. However, time to conception and treatment costs were significant (both $P < 0.001$) between groups. Paired comparisons found that the three groups treated with AIH had the longest time to conception and highest treatment cost. In the two groups treated with auxiliary use of prodom and syringes, time to conception was the shortest and the treatment cost was minimal; In the four groups with traditional treatment, time to conception and the treatment cost exhibited intermediate results. The differences were statistically significant (all $P < 0.001$) between the PACT group vs the AIH group, the SACT group vs the AIH group, and the TT group vs the AIH group.

Table 4. Association of different treatment measures with pregnancy and time to conception in the first stage treatment

Variables	Pregnancy					Time to conception				
	Number	P^1 value	OR	P^2 value	95% CI	Month (mean ± SD)	P^3 value	OR	P^2 value	95% CI
Auxiliary use of prodom										
YES	58	**< 0.001**	2.649	**0.010**	1.263-5.747	4.57±2.04	**< 0.001**	0.338	**< 0.001**	0.239-0.478
NO	51					>6				
Auxiliary use of syringe										
YES	40	**< 0.001**	1.305	0.312	0.779-2.188	4.85±1.87	0.001	0.991	0.928	0.817-1.102
NO	44					>6				
Traditional therapy										
YES	20	**0.022**	0.318	**< 0.001**	0.178-0.567	5.75±1.86	**< 0.001**	1.302	**0.034**	1.021-1.661
NO	61					>6				
Chymotrypsin therapy										
YES	98	**< 0.001**	3.146	**< 0.001**	1.764-5.611	4.69±1.97	**< 0.001**	0.768	**0.034**	0.602-0.980
NO	95					>6				

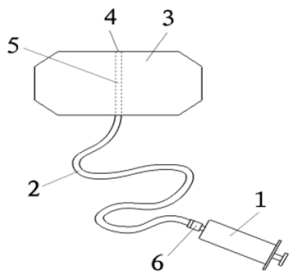
Abbreviations: OR, odds ratio; CI, confidence interval. [1]*P*-values were calculated using chi-square; [2]*P*-values were calculated using multivariate logistic regression analysis, adjusted for age; [3]*P*-values were calculated using *t*-test; The boldface represents statistical significance.

Table 5. Association of different treatment measures with pregnancy and time to conception in the second stage treatment

Variables	Pregnancy					Time to conception				
	n	P^1 value	OR	P^2 value	95% CI	Month (mean ± SD)	P^3 value	OR	P^2 value	95% CI
Auxiliary use of prodom										
YES	35	**0.001**	1.438	0.283	0.741-2.791	9.714±2.641	**< 0.001**	0.776	**0.003**	0.658-0.916
NO	22					>36				
Auxiliary use of syringe										
YES	23	0.497	1.294	0.498	0.614-2.724	11.087±3.088	**0.013**	0.823	**0.042**	0.682-0.993
NO	15					>36				
Traditional therapy										
YES	31	**0.009**	0.426	0.051	0.223-0.814	12.065±2.144	**0.012**	0.934	**0.02**	0.882-0.989
NO	39					>36				
Chymotrypsin therapy										
YES	58	0.097	1.73	0.099	0.903-3.314	10.259±2.881	**< 0.001**	0.709	**0.001**	0.581-0.866
NO	37					>36				
AIH										
YES	21	0.890	1.054	0.890	0.501-2.218	33.191±7.312	**< 0.001**	1.491E11	0.997	0.000-
NO	16					>36				

Abbreviations: AIH, artificial insemination with husband's semen; OR, odds ratio; CI, confidence interval. [1]*P*-values were calculated using chi-square; [2]*P*-values were calculated using multivariate logistic regression analysis, adjusted for age; [3]*P*-values were calculated using *t*-test; The boldface represents statistical significance.

group. The pregnancy rate was 70% (14/20), time to conception was 9.43±2.28 months, and treatment cost was $ 2,339±250 in the TT group that was changed to the SACT group. The pregnancy rate was 66.67% (8/12), time to conception was 35.75±8.08 months, and treatment cost was $ 21,747±3,533 in the TT group that was changed to the AIH group. There were no significant differences ($P = 0.141$) in pregnancy rates. However, time to conception and treatment costs were significant (both $P < 0.001$) between groups. Paired comparisons found that the three groups treated with AIH had the longest time to conception and highest treatment costs. In the two groups treated with auxiliary use of prodom and syringes, time to conception was the shortest and treatment costs were minimal. In the four groups with traditional treatment, time to conception and treatment costs exhibited intermediate results. Differences were statistically significant (all $P < 0.001$) between the PACT group and AIH group, the SACT group and AIH group, and the TT group and AIH group.



1. The detachable syringe
2. The drug infusion catheter(Length 480 mm/ Tube outer diameter 2 mm/ Tube inner diameter 0.8 mm)
3. The polyurethane film (PU film, Specifications for 90 mm × 60 mm)
4. The outlet of the drug infusion catheter
5. The drug infusion catheter is attached to the part 3
6. The connection between the drug infusion catheter and the detachable syringe

Figure 1. Schematic diagram of a new type of assisted reproductive device (Prodom).

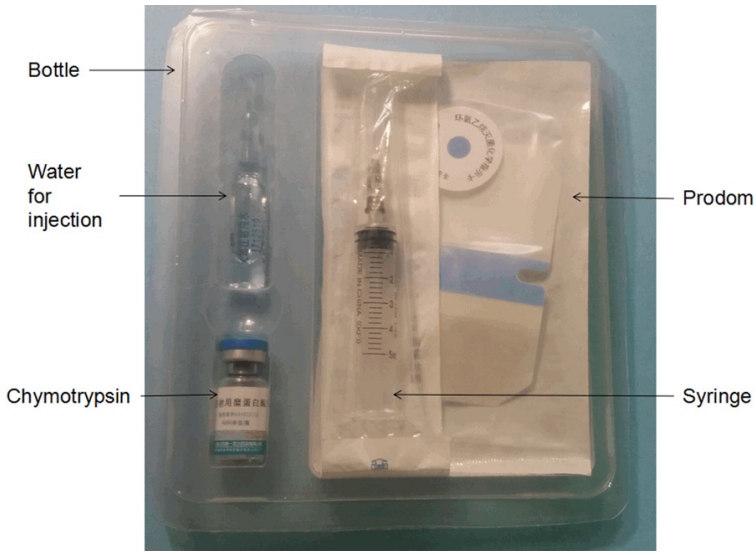


Figure 2. Photos of packing sample product label of a new type of assisted reproductive device (Prodom).

Association in different treatment measures with pregnancy and time to conception in the first/second stage treatment

As shown in **Table 4**, for patients effectively treated by the first stage of treatment, there was a correlation after adjusting for age between using prodom with the pregnancy (OR = 2.649, 95% CI: 1.263-5.747, $P < 0.010$) and time to conception (OR = 0.338, 95% CI: 0.239-0.478, $P < 0.001$). Similarly, there was an association between traditional therapy and pregnancy (OR = 0.318, 95% CI: 0.178-0.568, $P < 0.001$) and time to conception (OR = 1.302, 95% CI: 1.021-1.661, $P = 0.034$), as well as an association between chymotrypsin therapy with pregnancy (OR = 3.146, 95% CI: 1.764-5.611, $P < 0.001$) and time to conception (OR = 0.768, 95% CI: 0.602-0.980, $P = 0.034$). However, it was not obvious that the auxiliary use of the syringe was associated with pregnancy rates (OR = 1.305, 95% CI: 0.779-2.188, $P = 0.312$) and time to conception (OR = 0.991, 95% CI: 0.817-1.102, $P = 0.928$). Additionally, as shown in **Table 5**, for patients that failed in the first stage treatment and were divided into the second stage treatment for treatment with other methods, there was a correlation after adjusting for age for auxiliary use of prodom (OR = 0.776, 95% CI: 0.658-0.916, $P = 0.003$), auxiliary use of a syringe (OR = 0.823, 95% CI: 0.682-0.993, $P = 0.042$), traditional therapy (OR = 0.934, 95% CI: 0.882-0.989, $P = 0.020$), and chymotrypsin therapy (OR = 0.709, 95% CI: 0.581-0.866, $P = 0.001$) with time to conception. However, there was no association in AIH (OR = 1.491E11, 95% CI: 0.000-, $P = 0.997$) with time to conception. Similarly, there was no clear correlation for auxiliary use of prodom (OR = 1.438, 95% CI: 0.741-2.791, $P = 0.283$), auxiliary use of a syringe (OR = 1.294, 95% CI: 0.614-2.724, $P = 0.498$), traditional therapy (OR = 0.426, 95% CI: 0.223-0.814, $P = 0.051$), chymotrypsin therapy (OR = 1.730, 95% CI: 0.903-3.314, $P = 0.099$), and AIH (OR = 1.054, 95% CI: 0.501-2.218, $P = 0.890$) with pregnancy.

In terms of correlation analysis of various treatment measures used for increasing pregnancy rates and shortening time to conception, prodom was associated with increased pregnancy rates (OR = 2.649, 95% CI: 1.263-5.747, $P < 0.010$) and shortened time to conception (OR = 0.338, 95% CI: 0.239-0.478, $P < 0.001$) in the first stage treatment. However, in second stage treatment, prodom was associated with shorter time to conception only (OR = 0.776, 95% CI: 0.658-0.916, $P = 0.003$), after

adjusting for age, chymotrypsin, traditional drug therapy, and AIH effects.

Discussion

The present study evaluated the clinical efficacy of a new type of assisted reproductive device, prodom. This device assists in the administration of chymotrypsin to the spouse's vagina and synchronizes with ejaculation. This can help in the treatment of ISL, which causes infertility. Results showed that the pregnancy rate was 53.21% in the PACT group, higher than that of both the SACT group (47.62%) and TT group (24.69%). Time to conception was 4.57±2.04 months, lower than that of both the SACT group (4.85±1.87 months) and TT group (5.75±1.86 months). Moreover, overall cost of treatment ($ 1,723±721) in the PACT group was relatively small. Results showed that the new assisted reproductive device could assist chymotrypsin in the treatment of male infertility caused by ISL through *in vitro* administration of drugs. The therapeutic effects were better than existing treatment.

At present, there are many ways to treat ISL, including oral administration, muscle injection, transurethral administration, transrectal administration, transvaginal administration, and acupuncture. All treatment methods have been reported to have certain effects, but with limitations, causing some patients to never achieve satisfactory results. Previous studies have confirmed that the addition of chymotrypsin into the semen after *in vitro* ejaculation can completely correct ISL and improve sperm vitality without damaging sperm quality. Additionally, the present team once used a syringe to assist the injection of chymotrypsin into the vagina of the spouse when couples have sex to treat male infertility caused by ISL, achieving a certain effect. However, the syringe injection process may cause inconvenience and a degree of pain to the spouse, which makes some patients and spouses unwilling to receive the treatment. As shown in **Table 1**, of the 63 patients that halted treatment, the PACT group accounted for 12.80% (16/125), the SACT group accounted for 29.41% (35/119), and the TT group accounted for 12.90% (12/93). Moreover, the rate of abandoning treatment in the PACT group was lower than that in the other two groups and differences were statistically significant (P = 0.002). This finding shows that the clinical application of prodom has certain advantages compared to existing treatment methods.

In the first stage of treatment, as shown in **Table 2**, in terms of pregnancy rates and time to conception, the PACT group was superior to the SACT group and TT group. In terms of treatment costs, the PACT group and SACT group were superior to the TT group, while differences between the PACT group and SACT group were not statistically significant. Moreover, the PACT group and SACT group belonged to local treatment, while the TT group belonged to traditional systemic treatment. Results suggest that local treatment (including PACT and SACT) is superior to traditional systemic treatment. As shown in **Table 3**, after 9 months, for unfertilized patients in the first stage treatment that failed, the treatment methods were replaced with other treatment methods. The patients were also grouped according to their treatment method and classified as the second stage. In terms of time to conception and treatment costs, the PACT group, SACT group, and TT group were superior to the AIH group. In terms of pregnancy rates, there were no statistically significant differences among the groups. As shown in **Tables 4** and **5**, prodom was associated with increased pregnancy rate (OR = 2.649, 95% CI: 1.263-5.747, P < 0.010) and shortened time to conception (OR = 0.338, 95% CI: 0.239-0.478, P < 0.001) in the first stage treatment. However, in the second stage treatment, prodom was associated with shorter time to conception only (OR = 0.776, 95% CI: 0.658-0.916, P = 0.003). Notably, chymotrypsin plays a key role in improving ISL. However, clinical treatment differences may arise because of different prescribing practices of chymotrypsin. This finding also shows that the clinical application of prodom has advantages over existing treatment methods.

The prodom described in this study was mainly composed of polyurethane film (PU film) and an injection catheter. It was coated with pressure-sensitive adhesive on the inner side of the PU film (see **Figures 1** and **2**). The prodom operating process was as follows: 1) Before sex between the husband and wife, 1 mL of sterile saline and chymotrypsin solution was injected with a syringe, while the prodom was pasted

onto the erect penis with the pressure-sensitive adhesive set of PU film; 2) Chymotrypsin injection into the partner's vagina was synchronized with ejaculation and the chymotrypsin was blended with sperm in the vagina. This study introduced the new treatment through clinical application and compared it with previous methods (used syringes, auxiliary to the chymotrypsin, in the vaginal injection method before and after sex, as well as the traditional treatment comparison [3, 5, 7, 8, 14-16, 23, 26, 32, 33]) and costs of treatment reported in the current literature [34-40]. Results confirm that this method has the following advantages: (1) The device has a simple structure and is easy to use. It is economical and practical; (2) The treatment is superior to previous treatments. Pregnancy rates of the spouse are increased and time to conception is shortened; (3) After the failure of the traditional treatment, the replacement and combination of the new treatment method remains effective. Similarly, when the new treatment fails, the combination of traditional treatment remained effective; and (4) Compared with traditional treatment methods (including AIH), when the husband and wife have sex, the prodom injection is synchronized with ejaculation. It can ensure that semen fully contacts with chymotrypsin and prevents semen leakage from the vagina. This new treatment method can meet the goal of restoring the fertility of male infertility patients while allowing full enjoyment of the pleasures of sexual life.

Previous studies have reported that the pregnancy rate obtained by improving ISL through Chinese Medicine treatment was 38.71% [8], while the pregnancy rate obtained by improving ISL through chymotrypsin was between 21% and 25% [21, 22]. The pregnancy rate reported in this study was 53.21% using PACT and 47.62% with SACT, both of which were higher than in previous reports. There have been few studies reporting on the time to conception and cost of treatment. Results of the current study are valuable and the new method is worthy of recommendation.

However, the present study had several limitations. The overall pregnancy rate was 74.82% (205/274), which means that 25.72% (69/274) of patients did not benefit from the existing treatment. New treatment methods should be further explored [32, 33]. Furthermore, this study was conducted only in a Chinese population, which included a majority of Han Chinese people and a small proportion of Hui, Miao, Buyi, and Gelao people, all with different life backgrounds. The current study did not subdivide the participants. This study was based on only single-center clinical data and a relatively small number of cases. These limitations may have influenced results and conclusions. Hence, larger and more centralized case studies are necessary.

Conclusion

Results of the current study indicate that prodom assists in the administration of chymotrypsin to the spouse's vagina. It can increase the rate of pregnancy and shorten the time to conception in patients with ISL. This study concludes that prodom can effectively assist chymotrypsin in the treatment of male infertility caused by ISL.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

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References

[1] World Health Organization. WHO laboratory manual for the examination and processing of human semen, 5th edn. Geneva: World Health rganization, 2010.

[2] Liu FX, Su DL, Zhu GY. [Abnormal semen liquefaction and seminal plasma lipoprotein (a)]. Zhonghua Nan Ke Xue 2013; 19: 247-50.

[3] Citrino G, Check JH, Diantonio A, Bollendorf A, Katsoff D. Pretreatment of sperm with low hypo-osmotic swelling tests with chymotrypsin prior to intrauterine insemination (IUI) and avoidance of unprotectected intercourse results in pregnancy rates comparable to IUI for other male factor problems. Clin Exp Obstet Gynecol 2010; 37: 187-9.
[4] Check JH. Antisperm antibodies and human reproduction. Clin Exp Obstet Gynecol 2010; 37: 169-74.
[5] Xiong GB, Yao WL, Wu FH. [Shenfu Qiangjing decoction improves non-inflammatory and non-liquefied semen in kidney-yang deficiency men]. Zhonghua Nan Ke Xue 2009; 15: 1138-41.
[6] Check JH. Treatment of male infertility. Clin Exp Obstet Gynecol 2007; 34: 201-6.
[7] Check ML, Katsoff D, Check JH, Summers-Chase D. Effect of treating sperm with low hypo-osmotic swelling test scores with chymotrypsin on pregnancy rates after conventional in vitro fertilization-embryo transfer. Fertil Steril 2004; 82: 741-2.
[8] Peng S, Zheng Y, Zheng K, Lin K, Wu J, Zheng W, Li Y, Li Y, Lin C. Effect of a comprehensive therapy plus gushenyutai plaster administered at guanyuan (CV 4) on male infertility associated with semen non-liquefaction. J Tradit Chin Med 2014; 34: 666-72.
[9] Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril 2008; 89: 1603.
[10] Eisenberg ML, Lathi RB, Baker VL, Westphal LM, Milki AA, Nangia AK. Frequency of the male infertility evaluation: data from the National Survey of Family Growth. J Urol 2013; 189: 1030-4.
[11] Hadwan MH, Almashhedy LA, Alsalman AR. Study of the effects of oral zinc supplementation on peroxynitrite levels, arginase activity and NO synthase activity in seminal plasma of Iraqi asthenospermic patients. Reprod Biol Endocrinol 2014; 12: 1.
[12] Majumdar G, Majumdar A. A prospective randomized study to evaluate the effect of hyaluronic acid sperm selection on the intracytoplasmic sperm injection outcome of patients with unexplained infertility having normal semen parameters. J Assist Reprod Genet 2013; 30: 1471-5.
[13] Karamahmutoglu H, Erdem A, Erdem M, Mutlu MF, Bozkurt N, Oktem M, Ercan DD, Gumuslu S. The gradient technique improves success rates in intrauterine insemination cycles of unexplained subfertile couples when compared to swim up technique; a prospective randomized study. J Assist Reprod Genet 2014; 31: 1139-45.
[14] Gatimel N, Parinaud J, Leandri RD. Intracytoplasmic morphologically selected sperm injection (IMSI) does not improve outcome in patients with two successive IVF-ICSI failures. J Assist Reprod Genet 2016; 33: 349-355.
[15] Ziebe S, Devroey P. Assisted reproductive technologies are an integrated part of national strategies addressing demographic and reproductive challenges. Hum Reprod Update 2008; 14: 583-92.
[16] Check JH, Hourani W, Check ML, Graziano V, Levin E. Effect of treating antibody-coated sperm with chymotrypsin on pregnancy rates following IUI as compared to outcome of IVF/ICSI. Arch Androl 2004; 50: 93-5.
[17] Yoshida K, Yamasaki T, Yoshiike M, Takano S, Sato I, Iwamoto T. Quantification of seminal plasma motility inhibitor/semenogelin in human seminal plasma. J Androl 2003; 24: 878-84.
[18] Check ML, Kiefer D, Check JH, Hourani W, Long R. Treatment of sperm with subnormal host scores with chymotrypsin/viable pregnancy after IUI. Arch Androl 2002; 48: 155-8.
[19] Check JH, Katsoff D, Check ML, Choe JK, Swenson K. In vitro fertilization with intracytoplasmic sperm injection is an effective therapy for male factor infertility related to subnormal hypo-osmotic swelling test scores. J Androl 2001; 22: 261-5.
[20] Tremblay RR, Coulombe E, Cloutier S, Brunet C, Deperthes D, Frenette G, Dubé JY. Assessment of the trypsin-like human prostatic kallikrein, also known as hK2, in the seminal plasma of infertile men: respective contributions of an ELISA procedure and of Western blotting. J Lab Clin Med 1998; 131: 330-5.
[21] Katsoff D, Check JH, Bollendorf A, Benfer K. Chymotrypsin-galactose treatment of sperm with antisperm antibodies results in improved pregnancy rates following in vitro fertilization. Am J Reprod Immunol 1995; 33: 149-54.
[22] Bollendorf A, Check JH, Katsoff D, Fedele A. The use of chymotrypsin/galactose to treat spermatozoa bound with anti-sperm antibodies prior to intra-uterine insemination. Hum Reprod 1994; 9: 484-8.
[23] Honea KL, Houserman VL, Merryman DC, Free DA, Stringfellow SE. Effect of limited proteolysis with alpha-chymotrypsin on semen with an abnormal sperm penetration assay and possible application for in vitro fertilization or intrauterine insemination. J Assist Reprod Genet 1993; 10: 255-60.
[24] Pattinson HA, Mortimer D, Taylor PJ. Treatment of spermagglutination with proteolytic en-

zymes. II. Sperm function after enzymatic disagglutination. Hum Reprod 1990; 5: 174-8.
[25] Nag Das SK, Bhattacharyya A. Enzymic activities in the seminal plasma of normospermic, oligospermic and infertile azoospermic men. Enzyme 1984; 32: 157-61.
[26] Freischem CW, Bordt J, Hanker JP, Schneider HP, Nieschlag E. [Pregnancy after treatment of ejaculate with alpha-chymotripsine because of failure to liquefy]. Geburtshilfe Frauenheilkd 1983; 43: 490-1.
[27] Gecse A, Ottlecz A, Török L, Telegdy G, Morvay J, Sas M. Bradykininase and protease inhibitors in seminal plasma of fertile and infertile men. Arch Androl 1979; 2: 311-6.
[28] Syner FN, Moghissi KS, Yanez J. Isolation of a factor from normal human semen that accelerates dissolution of abnormally liquefying semen. Fertil Steril 1975; 26: 1064-9.
[29] Retzke U, Wilken H. [Complications following hydrotubations with alpha-chymotrypsin]. Geburtshilfe Frauenheilkd 1968; 28: 1035-7.
[30] Koistinen H, Soini T, Leinonen J, Hyden-Granskog C, Salo J, Halttunen M, Stenman UH, Seppälä M, Koistinen R. Monoclonal antibodies, immunofluorometric assay, and detection of human semenogelin in male reproductive tract: no association with in vitro fertilizing capacity of sperm. Biol Reprod 2002; 66: 624–628.
[31] The state intellectual property office of the People's Republic of China, ZL201420827963.4, an auxiliary reproductive device, 2014/12/24.
[32] Meng MV, Greene KL, Turek PJ. Surgery or assisted reproduction? A decision analysis of treatment costs in male infertility. J Urol 2005; 174: 1926-31.
[33] Kolettis PN, Sabanegh ES. Significant medical pathology discovered during a male infertility evaluation. J Urol 2001; 166: 178-80.
[34] Bitler MP, Schmidt L. Utilization of infertility treatments: the effects of insurance mandates. Demography 2012; 49: 125-49.
[35] Dupree JM, Dickey RM, Lipshultz LI. Inequity between male and female coverage in state infertility laws. Fertil Steril 2016; 105: 1519-22.
[36] Ministry of Health and Long-Term Care. Improving Access to Safe Fertility Treatments; 10 April, 2014. Available from: http://www.news.ontario.ca/mohltc/en/2014/04/improving-access-to-safe-fertility-treatments.html. [Last accessed on 2015 Oct 24].
[37] Québec Assisted Reproduction Program. Available from: http://www.sante.gouv.qc.ca/en/programmes-et-mesures-daide/programme-quebecois-de-procreation-assistee/description/. [Last accessed on 2015 Oct 24].
[38] Dupree JM. Insurance coverage for male infertility care in the United States. Asian J Androl 2016; 18: 339-41.
[39] Chandra A, Copen CE, Stephen EH. Infertility service use in the United States: data from the National Survey of Family Growth, 1982-2010. Natl Health Stat Report 2014; 73: 1-21.
[40] Elliott PA, Hoffman J, Abad-Santos M, Herndon C, Katz PP, Smith JF. Out of pocket costs of male infertility care and associated financial strain. Urol Pract 2016; 3: 256-261.