Research Report

Effect of clomiphene citrate on the quality of cervical mucus in infertile women

Pengaruh pemberian klomifen sitrat terhadap kualitas getah serviks pada perempuan infertil

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Abstract

Objective: To describe the effect of clomiphene citrate on the quality of cervical mucus in infertile women.

Method: This study is a non-randomized clinical trial. The study was carried out at several education hospitals in Makassar from March 2008 to April 2009. The subjects of the study were infertile women who fulfilled the inclusion criteria with intervention study. The statistical analysis was performed using Wilcoxon Sign-ed Rank Test with α 5%.

Result: There were 36 cases found, and most were in the range of 26 - 30 years old (38.9%), university level education (50%), civil servant (47.2%), normal nutritionals status (55.5%), regular menstruation cycle (94.4%), marriage length 1 - 5 years (52.8%), and previously treated (61.1%). There was a significant difference of the cervical mucus quality in the infertile women before and after the administration of clomiphene citrate which tend to become worse ($p = 0.012$). At previously CC-treated group, it was found that after the administration of clomiphene citrate, the quality of cervical mucus tend to be worse (100%).

Conclusion: The administration of clomiphene citrate tends to have declining effect on cervical-mucus quality of infertile women.

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Keywords: clomiphene citrate, quality of cervical mucus, infertile women

Abstrak

***Tujuan**: Untuk mengetahui pengaruh pemberian klomifen sitrat terhadap kualitas getah serviks perempuan infertil.*

***Metode**: Penelitian ini merupakan Non-Randomized Clinical Trial. Dilakukan pada beberapa rumah sakit pendidikan di Makassar dari Maret 2008 sampai April 2009. Subjek penelitian adalah perempuan infertil yang memenuhi kriteria inklusi yang merupakan studi intervensi. Analisis statistik dengan menggunakan Wilcoxon Signed Rank Test dengan α 5%.*

***Hasil**: Didapatkan 36 kasus perempuan infertil, dengan karakteristik terbanyak pada usia 26 - 30 tahun (38,9%), pendidikan setingkat perguruan tinggi (50%), pekerjaan PNS (47,2%), status gizi normal (55,5%), siklus haid teratur (94,4%), lama menikah 1 - 5 tahun (52,8%), riwayat pernah berobat (61,1%). Perubahan kualitas getah serviks sebelum dan setelah pemberian klomifen sitrat cenderung menjadi jelek ($p = 0,012$). Pada kelompok yang pernah berobat, didapatkan perubahan kualitas getah serviks yang menjadi jelek setelah pemberian klomifen sitrat (100%).*

***Kesimpulan**: Pemberian klomifen sitrat menyebabkan penurunan kualitas getah serviks perempuan infertil.*

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***Kata kunci**: klomifen sitrat, kualitas getah serviks, perempuan infertil*

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INTRODUCTION

Infertility is defined as inability to have or to achieve pregnancy and/or to maintain a pregnancy to reach sufficient month after 12 months or after regular coitus without any contraception.[1,2]

In United States, the infertility occurrence rates are around 10 - 15% on reproduction age. In Indonesia, it was estimated 12% couples were unable to have a live child. Therefore, approximately 3 million individual infertile couples are living across Indonesia.[3,4]

The real incidence of general factors are extremely varied. In general, infertility could be caused by anovulatory cycle (10 - 15%), pelvic factor (30 - 40%), abnormalities of male reproduction tract (10 - 15%), cervical factor (10 - 15%), and unknown factors.[1,5,6]

Cervical factors can be caused by the obstruction of the cervical canal tract, abnormality of the cervical mucus, cervical malposition, or a combination of any of those factors. The cervix actually has an important role in the capacity and sperm transport after coitus. Cervical mucus assessment can be used as a liable checking procedure in order to detect ovulation. The amount of production, and the characteristic of cervical mucus are always changed based on the estrogen concentration during follicular phase.[1,7]

Cervical mucus has a physical and chemical alteration based on the menstruation cycle phase. During proliferation phase to ovulation, the estrogen concentrations will stimulate the mucous formation. Moreover, the cervical mucus will be diluted by the decreased level of albumin and increased level of water and mucin. The decreased viscosity of cervical mucus during ovulation increase the capacity of sperm to penetrate the cervical mucus. After ovulation, there will be high progesterone concentrations which will block the secretion activity of epithelial cells, resulting on the increase of cervical mucus viscosity and density.[5,7,8]

Cervical mucus assessment can be used as parameter to identity ovulation. Maximum score for cervical mucus is 15. Score higher than 10 indicates a good cervical mucus, which is easier to penetrate by sperm, less than 10 score indicating a poor cervical mucus

Table 1. Scoring for cervical mucus quality.

score	volume	Consistency	Ferning	spinn-barkeit	cell-composition
0	0 ml	Thick, good viscosity	No crystallization	< 1 cm	> 20 cells/LPK - or > 1000 cells/mm^3
1	0.1	Average Thickness	Atypical	1 - 4 cm	11 - 20 cells/LPK - or 501 - 1000 cells/mm^3
2	0.2	Less Thickness	Primary and secondary stem	5 - 8 cm	1 - 10 cells/LPK or 1 - 500 cells/mm^3
3	≥ 0.3	Fluid	Tertiary and quarter stem	≥ 9 cm	0 cell/LPK

condition. This scoring for cervical mucus condition or quality is based on the system developed by Moghissi (1976), which is based on original proposal initiated by Insler and colleague (1972) as shown on Table 1.[7]

Ovulation induction is a medical procedure to help infertile women who suffer from hypothalamus pituitary-ovarian axis dysfunction (anovulatory cycle). The most popular stimulation agent which has been used until now is clomiphene citrate. Based on the real fact, out of 80 - 85% of previously treated women will have the ovulation, and 40% of these ovulated women will have pregnancy.[3,9]

The definite mechanism of clomiphene citrate is still unknown. It is predicted that the anti-estrogenic nature of clomiphene citrate might occupy estrogen receptors in the hypothalamus and pituitary, resulting in excretion of FSH and LH from pituitary. The increment of gonadothropin level will sufficiently induce follicular maturation andovulation. The mechanism of action of clomiphene could induce the production of endogenous estrogen.[9,10]

Clomiphene citrate has a good tolerability. However, some mild adverse effects could be found eventhough these are rarely become so serious that the patient should discontinue the administration. Hot flushes and mood alteration are regularly found. Morover, tension sensation on pelvic pain, visual distubance vomiting, and nausea sensation are rarely found. Clomiphene citrates also have several effect on the breast (tension sensation of breast), endocervix (poor cervical mucus quality), endometrium (blocking the endometrium development), and ovaries (causing a spontaneous abortion). However, there was no data supports the statement that clomiphene citrate could induce significant clinical consequences.[9,11,12]

The poor quality of cervical mucus is one of side-effects of clomiphene citrate as a consequence of its anti-estrogenic nature. The alteration of cervical mucus can cause motility disruption of sperm. The adverse effect of clomiphene citrate to particular reproductive organ might cause poor pregnancy figures, despite good ovulation rate. However, the effect of clomiphene citrate has still been argued.[11,13]

The indistinct condition and the fact that there were no sufficient data regarding the quality of cervical mucus assessment before and after clomiphene citrate administration in Indonesia, particularly in Makassar lead us to conduct this study.

METHODS

This study is a Non-Randomized Clinical Trial to observe the effect of clomiphene citrate administration on the cervical mucus quality of infertile woman. The study was held at several educational hospitals in Makassar.

The sample population of this study was calculated using Isaac and Michael formula, and 36 cases were found. Samples were collected from population using non-random sampling method, which had fulfilled the inclusion and exclusion criteria. The inclusion criteria were age ranged 20 - 40 years old, normal sperm analysis, regular and irregular menstrual cycle, no anatomical abnormalities, no history of gynecological operation, no history of tumor/cancer or similar condition in family medical history, and agree to participate in this study.

Recruited patients underwent initial cervical assessment during their fertile period (after being confirmed bt LH test) clomiphane citrate 1 x 50 mg was started on the second day of menstruation for 5 days and 5 days after finished the drug patients underwent second LH monitoring. If LH test was positive, patients were asked to undergo the second cervical mucus assessment.

Cervical mucus sample was taken while patients was lying in lithotomy position. Tuberculin hypodermic needle 1 cc was used to aspirate the servical mucus. Assessment was done as soon as possible, pH evaluation was done using pH dipstic. Moreover, cervical mucus will be observed under the microscope to asses turning formation and cell composition.

The cervical mucus quality were then assessed using moghissi scores. If the score is ≤ 10, it is regarded that the cervical mucus have a poor quality, if the score is > 10, the cervical mucus is regarded to have a good quality. The result was recorded in study forms and analyzed using Wilcoxon Signed Rank Test.

RESULT

Thirty six infertile women were recruited. Most of the patients aged between 26 - 30 years old (38.80%). Most of them are college graduated 50%, and 47.2% works as civil employed. Most subject have good nutrition. Duration of infertility were mostly between 1 - 5 years (52.8%) and most of them have experienced fertility treatment before (61.1%). (Tabel 2)

Initial cervical assessment showed 52.8% subject have good cervical mucus quality. On the contrary,

after cervical treatment, 77.8% of all subject showed poor quality cervical mucus. There was a significant alteron between cervical mucus quality.

Table 2. General Characteristic Distribution of Study Sample.

Characteristic	Total	
	N	%
Age (years)		
< 25	2	5.6
26 - 30	14	38.9
31 - 35	8	22.2
36 - 40	11	30.6
> 40	1	2.8
Education		
< 6	1	2.8
6 - 9	1	2.8
10 - 12	16	44.4
> 12	18	50.0
Occupation		
Housewives	15	41.7
Civil employee	17	47.2
Private employee	4	11.1
Nutritional status		
Poor (underweight)	-	0
Good (normal)	20	55.5
Excessive (overweight)	12	33.3
Obesity	4	11.1
Menstruation cycle		
Regular	34	94.4
Irregular	2	5.6
Years of marriage/infertile		
1 - 5 years	18	52.8
> 5 years	17	47.2
Previously treatment history		
Treatment	22	61.1
No treatment	14	38.9

Source: primary data

Sample distribution according to pH rate of cervical mucus before and after clomiphene citrate administration treatment, showed no significant differences. Highest pH rate of cervical mucus ranged from 6.1 - 8.0, either before clomiphene citrate administration (74.9%) or after the administration of clomiphene citrate (88.8%).

Between cervical mucus quality before and after clomiphene citrate administration there was a significant alteration ($p < 0.05$). It also show that most of cervical mucus qualities were declining after the administration of clomiphene citrate, as shown in 28 samples (77.8%). (Table 3)

Table 3. The comparative result of cervical mucus quality before and after clomiphene citrate administration treatment.

Final cervical mucus quality		Initial cervical mucus quality		total
		Poor	Good	
Poor	N (%)	1336.1	1541.7	2877.8
Good	N (%)	411.1	411.1	822.2
total	N (%)	1747.2	1952.8	36100

Wilcoxon Signed Rank Test with $p < 0.05$ ($p = 0.012$)

DISCUSSION

This study shows that most infertile woman were at the age of 26 - 30 years old. With Hutterites and other studies that stated this range of age (26 - 30 years old) is marked as the highest fertility age of women to have pregnancy. Older age will result in poorer fertility.

Cervical mucus pH rate before and after clomiphene citrate administration showed no significant differences. Highest pH rate was ranged from 6.1 - 8.0 for both conditions. This result was as expected due to the fact that cervical mucus pH rate was not affected by ovulated or non-ovulated cycle. Therefore, the result was not caused by the effect of clomiphene citrate administration.[1,7]

The quality alteration of the cervical mucus before and after clomiphene citrate administration tends to be worsen ($p < 0.05$). Table 3 shows that cervical mucus score which was initially poor remain to be poor after the treatment (36.1%), while the cervical mucus which has good score initially after cervical treatment showed declining of the mucus quality in 41.8% samples. In average, it shows that most of cervical mucus quality after clomiphene citrate tends to degrade, as happened in 77.8% samples.

Van Campenhout and colleague (1995) reported that the administration of clomiphene citrate for 25 - 50 mg/day dosage would partially block the enhancement of Spinnbarkeit of cervical mucus. Gysler and colleague (1995) found only 15% of their sample had poor cervical mucus quality. However, this study showed that there were 22.2% subject that which had good cervical mucus quality after clomiphene citrate administration in other hand, 11.1% samples showed poor cervical mucus quality before the treatment but have increased quality after the treatment. Due to these facts, it is assumed that this condition may be affected by various factors, including age, previously treatment history and sample collecting timing of sample collection.[1,13-15]

CONCLUSION

The administration of clomiphene citrate may cause worsening of cervical mucus quality. The administration of estrogen preparation along with clomiphene citrate might be considered, in repeated clomiphene citrate therapy.

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