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Research Article

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Treatment Experience of Shoseiryuto in Nine Cases of Coronavirus Disease 2019 in Pregnant Women: A Telephone Consultation - Second Report

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Abstract

Aim: *The coronavirus disease 2019 (COVID-19) pandemic has led to a significant increase in the number of pregnant women infected with the virus. Although various antiviral drugs are used in COVID-19 treatment, their safety in pregnant women remains uncertain. Kampo medicine is an insurance-covered, cost-effective, and safe medication in Japan, and its effectiveness in the treatment of COVID-19 has been previously reported. This study aimed to investigate the effects of shoseiryuto (SST) in the treatment of COVID-19 in pregnant women.*

Methods: *We conducted a retrospective case study on 13 pregnant women infected with COVID-19 from April 2022 to December 2022, and SST was prescribed for nine of these patients. The physical condition and obstetric symptoms of the patients were monitored by phone and SST was prescribed based on the theories of Shanghanlun and Jin Gui Yao Lue.*

Results: *Two patients were prescribed different Kampo medicines, one patient was prescribed Western medication, and another patient took a medical treatment at a different medical institution.*

The study found that the symptoms improved in eight patients after SST administration. The number of days required for improvement ranged from 2–6 d, with an average of 3.1 ± 3.4 d. SST administration was also effective in relieving obstetric symptoms in one patient.

Conclusion: *These findings suggest that SST may be effective in the treatment of COVID-19 in pregnant women.*

Keywords: COVID-19, Pregnant Women, Shoseiryuto, Kampo, Safety

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has now reached over 676 million cases worldwide and surpassed 33 million cases in Japan as of March 2023. The number of infections among pregnant women is also increasing, and we estimate that approximately 0.5% of all infections may occur during pregnancy. In the treatment of COVID-19 during the acute phase, multiple antiviral drugs are being used, and their effectiveness has been confirmed. However, molnupiravir has been reported to have effects such as decreased fetal weight, miscarriage, and malformations in fetuses. Additionally, concerns have been raised on the teratogenic effects of enzitofovir, which has been granted emergency approval [1]. Currently, the main treatment for pregnant women infected with COVID-19 is the administration of anti-inflammatory and pain relief medications such as paracetamol, and the circumstance prevents adequate treatment. Kampo is a cost-effective and safe medication that is covered by insurance in Japan. Several studies regarding the treatment of COVID-19 with Kampo medicine

have previously been published [2-4]. In a previous study, we have also reported a methodology and cases of the effectiveness of shoseiryuto (SST) in treating pregnant women infected with COVID-19 [5].

The primary objective of this study is to assess the efficacy and safety of Kampo medicine, specifically SST, in pregnant 9 patients infected with COVID-19 who present with cold-like symptoms. The main focus of the research is to determine whether Kampo medicine can be effective in managing COVID-19 symptoms during pregnancy and to provide insights into its safety profile.

2. Methods

The study sample comprises pregnant patients who were infected with COVID-19 between April 2022 and December 2022. Selection criteria for the sample were based on COVID-19 symptoms, gestational weeks, pregnancy history, and other clinical characteristics (Table).

	A	B	C	D	E	F	G	H	I
Age (yrs)	32	27	33	37	32	36	27	34	36
GA	30w1d	11w4d	18w5d	6w4d	30w0d	10w4d	20w3d	33w3d	11w2d
Para	Parous	Parous	Parous	Parous	Parous	Parous	Parous	Parous	Parous
CC	Cough(S)	Cough(S)	Cough(S)	Cough(S)	Cough (Mo)	Cough(S)	Cough(M)	Cough(S)	Cough(S)
Another C	Rhinorrhea	Rhinorrhea	Rhinorrhea	Pharyngitis	None	Septum	Rhinorrhea	Rhinorrhea	Pharyngitis
BT (℃)	37.2	36.7	37.5	36.9	36.7	36.4	36.2	37.0	37.7
SpO_2(%)	unknown	99	unknown	98	97	99	unknown	98	unknown
OB Symptom	Mild uterine contraction	none	none	none	none	none	none	none	none
Improvement	2DPD	4 DPD	2 DPD	3 DPD	2 DPD	No change	3 DPD	3 DPD	6 DPD
Institution	Other	Other	Other	Other	Other	Own	Own	Other	Other
Medical change	none	none	none	none	none	Change+	none	none	none
complication					hypo-thyroidism	asthma		asthma	

GA: gestational age, CC: Chief Complain, Another C: Another Complain, BT: Body Temperature, SpO2: percutaneous oxygen, OB: Obstetrics, DPD: days post-dose, S: severe, Mo: moderate, M: mild

Table: Individual Characteristic (Patient A~I)

Among the 13 pregnant women infected with COVID-19 managed our clinic, one opted for treatment at another healthcare facility, while another preferred Western medicine treatment. Additionally, two others expressed a preference for Kampo treatment, but were deemed ineligible for SST application. So, we prescribed another Kampo. The remaining nine women were enrolled in this study.

2.1. Constraints of the Study Design

This study is an observational case series and does not include a control group. When the study population consists of pregnant women, gathering a sufficient sample size can be exceedingly challenging, and establishing a control group can also be highly difficult. The absence of a control group is acknowledged as a limitation, and we address this limitation by discussing comparisons with other studies, relevance to existing literature, and alternative approaches within the study design. It is very difficult to conduct a double-blind trial in pregnant women.

2.1.1. Blinding

A double-blind trial was not conducted, and both the researchers and patients were aware of the treatment administered.

2.1.2. How to check the patients' condition

We checked the overall physical condition and obstetric symptoms of our nine patients via phone. Specifically, we asked about the presence and severity of symptoms such as body temperature, saturation of percutaneous oxygen (SpO2), cough, runny nose, and sore throat. As part of the obstetric check, we asked about the presence of uterine contractions, bleeding, and fetal movement in patients who were 20 weeks or more into their pregnancy.

Usually, when prescribing Kampo, the appropriate herbal formula

is selected for the patient based on diagnostic methods, such as tongue, pulse, and abdominal diagnosis, in traditional Kampo medicine. However, in this clinical study conducted through telephone consultations, tongue diagnosis, pulse diagnosis, and abdominal diagnosis were not possible. Therefore, the presence, severity, temporal progression of clinical symptoms, and the condition of the body, following the theories of Shanghanlun and Jin Gui Yao Lue [6]. The main symptoms in these nine cases were cough, rhinorrhea, sputum, and pharyngitis. Among the Shanghanlun and Jin Gui Yao Lue formulas, the candidate single-agent formulas considered were kakkonto, maoto, keishito, SST, shosaikoto, and saikokeishito. It was thought that many of the cases were being diagnosed over the phone, likely through health centers, and that some days had passed since the onset of symptoms.

2.1.3. Why SST was Chosen?

Therefore, based on the time elapsed, kakkonto and maoto were excluded. Keishito and saikokeishito were not chosen because these Kampo do not contain the Ephedra herb and were considered less effective. Shosaikoto is used for late yang stage pattern. Since Kampo medicine was selected to treat the early yang stage pattern, shosaikoto was excluded in this study. In other words, we conducted an intervention study in a restricted environment of telephone consultations, administering SST to 9 pregnant women infected with COVID-19 and exhibiting cold-like symptoms. According to the analysis report by Suzuki et al. from an administrative health database, the best commonly used formulas during pregnancy for cold-like symptoms were kakkonto, SST, etc. The authors also have extensive experience prescribing SST for cold-like symptoms during pregnancy, so, SST was selected for these nine cases [7].

In the description of the benefits of SST, it states that the covered symptoms include "watery phlegm, watery nasal discharge, nasal congestion, sneezing, wheezing, coughing, teary eyes: bronchitis, bronchial asthma, rhinitis, allergic rhinitis, allergic conjunctivitis, common cold." It was believed that SST could be sufficiently administered even under insurance coverage in Japan.

2.1.4. How to Prescribe and the Content of SST

Due consideration was given to the patient's medical history, including any cardiovascular diseases, since SST contains Ephedra herb [5]. After obtaining consent from the patient, we prescribed SST (a Tsumura medical extract), 9.0 g/d for 5 days. The daily dosage of SST is 9.0g and it consists of eight herbs.

The composition of the herbal ingredients is as follows: 6.0g of JP Pinellia Tuber (Pinellia ternate Breitenbach), 3.0g of JP Asiasarum Root (Asiasarum sieboldii F. Maekawa), 3.0g of JP Cinnamon Bark (Cinnamomum cassia J. Presl), 3.0g of JP Ephedra Herb (Ephedra sinica Stapf), 3.0g of JP Glycyrrhiza (Glycyrrhiza uralensis Fischer), 3.0g of JP Schisandra Fruit (Schisandra chinensis Baillon), 3.0g of JP Paeony root (Paeonia lactiflora Pallas), and 3.0g of JP Processed Ginger (Zingiber officinale Roscoe) [8].

2.1.5. Assessment of SST to Patients

We conducted daily health monitoring of the pregnant patients from our hospital by telephone until their discharge for home treatment. If their symptoms worsened or obstetric symptoms appeared, we had planned to switch to direct examinations; however, there were no such cases. For patients referred from other hospitals via the public health center, starting from the day after their visit to our hospital, public health nurses from the Akita City Public Health Center conducted health monitoring through the Health Center Real-time Information-Sharing System on COVID-19 or telephone contact. Clinical symptom evaluation, such as coughing, is usually assessed using a visual analog scale or numerical rating scale. However, to simplify the work and judgment of the public health nurses, we used "Severe," "Moderate," "Mild," and "Nothing" to rank the degree of symptoms from severe to non-existent. When the primary symptoms resolved, we concluded that SST administration was effective. Regarding the assessment of the effectiveness of SST on patients, constant communication and discussions were conducted with the public health nurses to ensure a rigorous evaluation of its effects. This clinical study was approved by the Ethics Committee of the Akita Medical Association (No.49, 2023.9.15).

3. Results

Individual characteristics are shown in Table. The study population included nine patients with gestational ages ranging from 6 to 33 weeks. Their ages ranged from 27 to 37 years, and the mean age was 32.0 ± 4.15 years. Patient A was reported in our previous report [5]. All patients were multiparous. The main symptom was cough, and according to the severity classification in the guidelines for the treatment of COVID-19 published by the Ministry of Health, Labour and Welfare, all cases were classified as mild [9]. Only Patient A showed obstetric symptoms, and mild uterine contractions were observed. Patient an experienced relief from cough symptoms and near disappearance of uterine contractions following SST administration.

Among the nine cases, SST showed effectiveness in eight cases. The number of days required for improvement ranged from 2–6 days, with an average of 3.1 ± 3.4 d. In contrast, in Patient F, SST was administered, but the cough persisted. This patient received treatment, such as inhalation medication, from another doctor and recovered. She had a history of asthma but was asymptomatic before pregnancy and was monitored without treatment. It was believed that asthma-like symptoms appeared and coughing persisted due to a new coronavirus infection. Patient H also had a history of asthma, but she already had inhalation medication on hand. Their symptoms improved with only the administration of SST from our clinic. None of the nine patients had adverse events, including side effects.

4. Discussion

The guidelines for the treatment of COVID-19 state that many pregnant women infected with the virus will have either no

symptoms or only mild symptoms [9]. However, some pregnant women may become severely ill in the latter half of pregnancy, leading to stillbirths or life-threatening situations [10]. However, these guidelines do not provide specific treatment options for pregnant women.

While some papers have described the effectiveness of Kampo for the treatment of COVID-19, very few reports are available regarding administering Kampo to pregnant women infected with the virus [2-4,11]. Although Kampo has been established for at least 1800 years, the safety of Kampo in pregnant women remains uncertain. One of the components of SST, the Ephedra herb, contains ephedrine, which promotes sweating and increases blood pressure; therefore, SST is categorized as an effective drug when the effectiveness surpasses the risk.

The daily dosage of SST contains 3 g of Ephedra herb, which is equivalent to 14.7 mg of ephedrine [12]. The recommended daily dose of ephedrine hydrochloride in "Attached document" and "Today's Therapeutic Drugs 2022" is 75 mg, and the ephedrine content in SST is within the standard range [13,14]. Additionally, according to the Briggs criteria for ephedrine hydrochloride administration during pregnancy, which categorizes drugs into "Compatible" as the safest option, SST containing Ephedra herb can be prescribed even during pregnancy. Therefore, it is believed that SST containing Ephedra herb can be prescribed even during pregnancy.

Suzuki et al. reported that Kampo prescriptions for pregnant women have become common. SST is thought to be prescribed more frequently in pregnant women with cold symptoms [7]. Furthermore, the research group led by Takayama et al. reported prescribing SST to patients with COVID-19 [15].

In the past 1800 years ago, when Shanghan Lun was established, it has been believed that Kampo formulations without Ephedra herb components have weaker effects against powerful infectious diseases, such as colds and COVID-19, which can be considered a modern form of Shanghan (Cold Damage) disease [6]. SST or kakkonto, which contain Ephedra herb, is commonly prescribed for colds during pregnancy, and we should consider selecting Kampo formulations containing Ephedra herb components for use during pregnancy.

5. Conclusion

In conclusion, this observational study aimed to evaluate the effectiveness and safety of Kampo medicine, specifically SST, in pregnant women with COVID-19 presenting cold-like symptoms. Despite the limited sample size, our findings suggest that SST administration in these cases resulted in a notable improvement in symptoms, with an average recovery time of 3.1 days. Importantly, no adverse events or side effects related to SST were observed in the study.

While the absence of a control group and the small sample size are acknowledged limitations of this study, the results provide preliminary evidence of the potential benefits of SST in the management of COVID-19 symptoms during pregnancy. Further research with larger sample sizes and rigorous study designs is warranted to confirm these findings and to establish guidelines for the use of Kampo medicine in pregnant women with COVID-19.

In light of the ongoing global pandemic, exploring safe and effective treatment options for pregnant women remains a crucial area of research. Our study contributes to this endeavor and underscores the need for continued investigation into the role of traditional medicine in combating COVID-19 during pregnancy.

Disclosure

Conflict of Interest

Hajime Nakae received honoraria from Tsumura & Co. The other authors declare no conflicts of interest.

Approval of the Research Protocol by an Institutional Reviewer Board and the Approval Number

The protocol for this research project has been approved by the Ethics Committee of Akita Medical Association and it conforms to the provisions of the Declaration of Helsinki. Approval No. 49.

Informed consent

Informed consent was obtained from all the participants.

Registry and the Registration No. of the study/trial

No.49 (2023.9.15)

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