View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 26–29

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Efficacy and safety of *daikenchuto* (TJ-100) in pregnant women with constipation

Hiroyuki Tsuda [a,*], Tomomi Kotani [a], Seiji Sumigama [a], Yukio Mano [a], Hiromi Hayakawa [b], Fumitaka Kikkawa [a]

[a] Department of Obstetrics and Gynecology, Nagoya University School of Medicine, Nagoya, Japan
[b] Department of Obstetrics and Gynecology, Kasugai Municipal Hospital, Kasugai-shi, Aichi, Japan

ARTICLE INFO

Article history:
Accepted 10 December 2014

Keywords:
constipation
constipation assessment scale
daikenchuto
pregnancy
trimester

ABSTRACT

Objective: Constipation is common and a significant problem in pregnant women. The purpose of this study was to examine the efficacy and the safety of *daikenchuto* in pregnant women with constipation.
Material and methods: This was a prospective study, and a total of 20 patients were registered between February 2010 and August 2012. The patients received 7.5 g/d of *daikenchuto* for 28 days from the day of registration. All enrolled patients were asked to complete the constipation assessment scale (CAS) every day. In addition, we measured the aspartate transaminase, alanine transaminase, blood urea nitrogen, and creatinine levels to assess the adverse effects of *daikenchuto*.
Results: The CAS scores were significantly lower at 28 days after *daikenchuto* treatment ($p = 0.019$), with a significant effect achieved on Day 1. The impact of the therapy was greatest in the second trimester ($p = 0.043$). No significant adverse effects of *daikenchuto* were observed, and the rates of preterm birth and pregnancy-induced hypertension were 10% and 5%, respectively, which are similar to previously reported values.
Conclusion: We herein demonstrated the efficacy and safety of *daikenchuto* in pregnant women with constipation. We hope that our findings will aid in the management of constipation in pregnant women.
Copyright © 2016, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Constipation is a significant problem in pregnant women and is often managed with a combination of stool softeners, laxatives, and dietary modifications (e.g. increased fiber intake) [1]. Although the frequency of stools is often improved with the above therapies, uncomfortable abdominal symptoms, such as abdominal distension and pain, often persist [2].

Daikenchuto (TJ-100), a traditional Japanese herbal medicine, is commonly used to treat adhesive bowel obstruction and chronic constipation [2,3]. This compound is composed of extract granules of Japanese pepper, processed ginger, ginseng radix, and maltose powder derived from rice. *Daikenchuto* extract powder (Tsumura & Co., Tokyo, Japan) is manufactured as an aqueous extract containing 2.2% Japanese pepper, 5.6% processed ginger, 3.3% ginseng, and 88.9% maltose syrup powder. The main ingredients of *daikenchuto* are hydroxy-alpha-sanshool (Japanese pepper), 6-shogaol (processed ginger), and ginsenoside Rb1 (ginseng radix). Contamination studies have certified *daikenchuto* to be free of unexpected pharmaceutical ingredients, toxins, pesticides, microbes, and heavy metals.

Treatment with *daikenchuto* has been reported to be effective for postoperative ileus [4], irritable bowel syndrome [5], and constipation in both children and Parkinson's patients [6,7]. Recently, evidence has accumulated regarding the following mechanisms of action of *daikenchuto*: the activation of endogenous adrenomedullin in patients with Crohn's disease [8], anti-inflammatory effects [9], increased gastrointestinal motility [10], and the upregulation of the blood flow in the colon [11]. The clinical efficacy of *daikenchuto* is now well established; however, there are no reports regarding its efficacy or safety in pregnant women with constipation.

The purpose of this study was to examine the efficacy of *daikenchuto* in pregnant women with constipation. In addition, we performed maternal blood tests focused on the liver and renal functions during treatment and assessed the outcomes of pregnancy in order to evaluate the safety of *daikenchuto*.

* Corresponding author. Department of Obstetrics and Gynecology, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
E-mail address: hiro-t@med.nagoya-u.ac.jp (H. Tsuda).

http://dx.doi.org/10.1016/j.tjog.2015.12.003
1028-4559/Copyright © 2016, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Materials and methods

Patients

This was a prospective interventional one-arm study conducted with the aim of determining the efficacy and safety of *daikenchuto* in pregnant women between February 2010 and August 2012 at Nagoya University Hospital, Nagoya, Japan. We excluded the patients with previous abdominal or pelvic surgery and finally registered a total of 20 healthy pregnant women suffering with constipation during this period. The patients received 7.5 g/day of *daikenchuto* for 28 days from the day of registration. In addition, we measured the aspartate transaminase (ALT), alanine transaminase (AST), blood urea nitrogen (BUN), and creatinine levels before and after treatment in order to assess the adverse effects of *daikenchuto*. All patients provided their written informed consent to participate in this study, which was approved by the Ethics Committee of Nagoya University Hospital.

Maternal and neonatal data were extracted from the patients' records, including maternal age, body mass index, gestational age at delivery, neonatal birth weight and sex, and umbilical pH at birth. Preterm delivery was defined as delivery at < 37 weeks of gestation. Pregnancy-induced hypertension was defined as the occurrence of gestational hypertension and proteinuria during pregnancy, with the reversal of these conditions after delivery. Gestational hypertension was defined as a systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg after 20 weeks of gestation in previously normotensive patients. Proteinuria was defined as a protein level above 300 mg on 24-hour urine collection.

Constipation assessment scale

The patients enrolled in this study were asked to complete the constipation assessment scale (CAS) every day. The CAS was introduced to determine whether an individual is experiencing constipation and assess the severity of the problem [12]. The scale consists of eight descriptors of constipation: (1) abdominal distension or bloating; (2) a change in the amount of gas passed rectally; (3) a reduced frequency of bowel movements; (4) liquid stools; (5) rectal fullness or pressure; (6) rectal pain during bowel movements; (7) small stools; (8) the inability to pass stool [12]. The patients was asked to rate whether the item is *no problem*, *some problem*, or a *severe problem*. *No problem* is scored as 0, *some problem* as 1, and *severe problem* is scored as 2. The patient was then asked to respond to each item, and the ratings are summed to obtain a total score, which ranges from 0, representing no problems with constipation, to 16, indicating severe constipation. Completing this scale takes less than 2 minutes on average.

Statistics

The data were entered into a spreadsheet (Excel; Microsoft Japan Co., Ltd., Tokyo, Japan), and SPSS was used for the data analysis (V.19.0; SPSS Japan Inc., Tokyo, Japan). The Wilcoxon signed-rank test was used to compare the CAS scores. In the box and whisker plot, the data are presented as the mean ± quartile deviation. A p-value of < 0.05 was considered to be significant.

Results

Maternal characteristics

The background characteristics of the patients are shown in Table 1. Aside from having constipation, all participants were healthy pregnant women. A total of six patients were in the first trimester (<14 weeks of gestation), eight patients were in the second trimester (14–27 weeks of gestation) and six patients were in the third trimester (> 28 weeks of gestation) at the time of registration. The rates of preterm birth and pregnancy-induced hypertension were 10% and 5%, respectively, which are similar to those reported [22] in pregnant Japanese women.

Effects of daikenchuto based on the CAS scores

We examined the CAS scores at before and after *daikenchuto* therapy (Figure 1). The CAS scores were significantly lower at 28 days after *daikenchuto* treatment ($p = 0.019$), indicating that *daikenchuto* significantly improves constipation in pregnant women. We then examined the CAS scores in each of the eight categories and found that abdominal distension or bloating, a reduced frequency of bowel movements and small stools each significantly improved after *daikenchuto* treatment ($p = 0.013$, 0.022, and 0.046, respectively).

Effects of daikenchuto based on the CAS scores in each trimester

We examined the CAS scores before and after *daikenchuto* therapy in each trimester (Figure 2). The CAS scores were significantly lower in the second trimester ($p = 0.043$); however, no significant differences were observed in the first and third trimesters ($p = 0.357$ and 0.273, respectively). Therefore, we concluded that *daikenchuto* is useful for treating constipation in pregnant women in the second trimester in particular.

Time course of the CAS scores

We examined the time course of the CAS scores, as shown in Figure 3. On Day 1 after the initiation of *daikenchuto* treatment, the CAS scores significantly improved ($p = 0.002$). Thereafter, the CAS scores did not differ significantly from those observed on Day 1. These results indicate that the effects of *daikenchuto* are noticed by patients the day after the start of treatment.

Evaluation of the safety of daikenchuto

We examined the AST, ALT, BUN, and creatinine levels before and after treatment. The mean levels of these parameters were as follows (before vs. after treatment): 16 IU/L versus 17 IU/L for ALT, 11 IU/L versus 12 IU/L for AST, 8.0 mg/dL versus 8.0 mg/dL for BUN, and 0.45 mg/dL versus 0.46 mg/dL for creatinine. No significant

Table 1
Maternal characteristics and outcomes of pregnancy.

	$n = 20$
Maternal background	
Maternal age (y)	35.0 (21–41)
Nulliparity	5 (25%)
Maternal body mass index	21.6 (17.9–26.7)
Pregnancy outcomes	
GA at delivery, weeks	38.0 (33–41)
Neonatal birth weight (g)	2730 (1906–3762)
Fetal growth SD	−0.1 (−1.8 to1.4)
Male neonate	90 (45%)
Umbilical artery pH	7.33 (7.20–7.44)
Preterm birth	2 (10%)
Pregnancy-induced hypertension	1 (5%)
Low birth weight infant (< 2500 g)	3 (15%)

Data are presented as the mean (range) or n (%).
BMI = body mass index; GA = gestational age; SD = standard deviation.

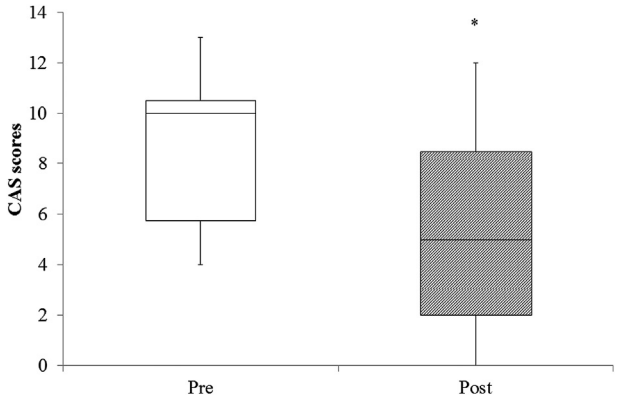

Figure 1. Constipation assessment scale (CAS) scores at before and after *daikenchuto* therapy. The CAS scores were significantly lower after *daikenchuto* treatment ($p = 0.019$), indicating that *daikenchuto* significantly improves constipation in pregnant women. The mean CAS score before and after treatment was 10.0 and 5.0, respectively.

adverse effects of *daikenchuto* were observed, and no patients exhibited abnormal values of the above parameters. During the treatment period, the clinical courses of both the mothers and fetuses were uneventful in all cases.

Discussion

This is the first study of the efficacy of *daikenchuto* in pregnant women with constipation. Our results showed that *daikenchuto* significantly improves the symptoms of constipation, including abdominal distension or bloating, a reduced frequency of bowel movements and small stools among the eight categories included in the CAS. *Daikenchuto* has been reported to decrease the volume of bowel gas in both male and nonpregnant female patients [2,13], similar to the effect observed among pregnant women in the present study. Therefore, we recommend treatment with *daikenchuto* in pregnant women suffering from constipation, primarily that complicated with abdominal distension. We also examined the period from the initiation of *daikenchuto* therapy with respect to improvements in constipation and found that the CAS scores significantly improved on Day 1 after the initiation of *daikenchuto* treatment. These results indicate that the effects of *daikenchuto* are noticeable to patients within one day after the start of treatment. We believe that this information provides useful advice for patients.

Furthermore, we examined the efficacy of *daikenchuto* in each trimester and observed a significant in the second trimester only. Although the CAS scores had a tendency to improve in the third trimester, the difference was not significant. We speculate that the following reasons may account for this phenomenon. First, the progesterone levels in pregnant women increase slowly during the first and second trimesters and rapidly during the third trimester. The level of progesterone has been reported to be a possible etiological factor for constipation [14–16]; therefore, the particular hormonal environment in the third trimester may explain the present results. Second, the uterus is largest in size in the third trimester, and bowel movements appear to be impaired due to compression of the uterus during this time. Lastly, the sample size was small in the present study. Among the six third trimester patients registered in this study, five exhibited improved CAS scores, while one showed disease exacerbation, with a decrease in the CAS score of 4–9. This may explain the lack of power to demonstrate a statistically significant difference. Therefore, a larger study is warranted to elucidate this issue. Similarly, no significant effects were noted in the first trimester. In the first trimester, some patients suffer from hyperemesis and symptoms such as nausea, vomiting and decreased food intake. In such circumstances, as well as under conditions of a hypovolemic state, the effects of *daikenchuto* on constipation may be limited.

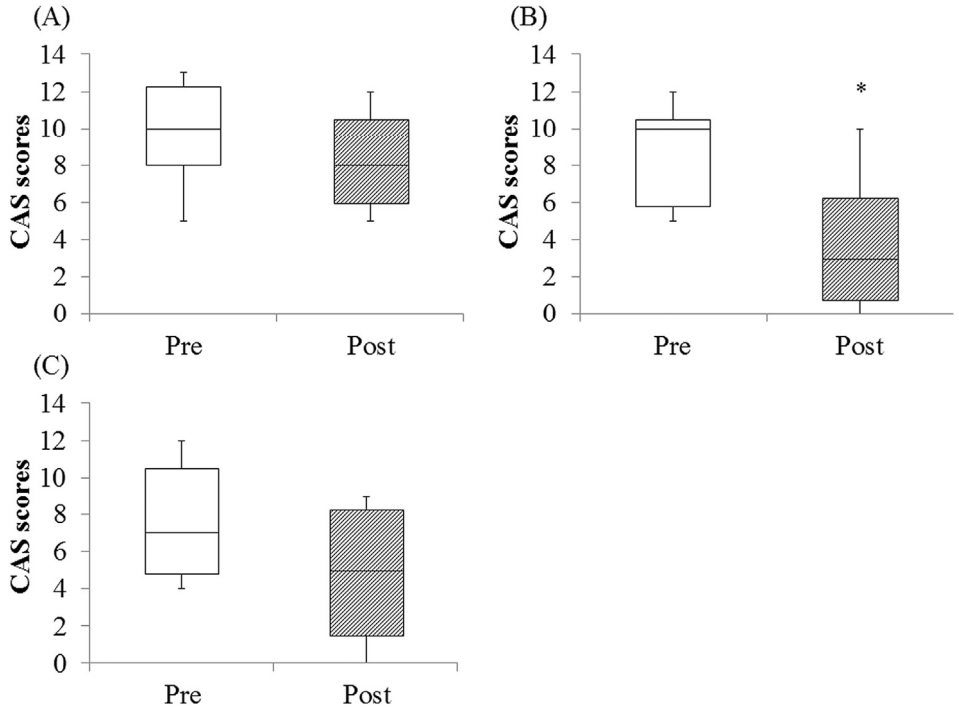

Figure 2. Constipation assessment scale (CAS) scores before and after *daikenchuto* therapy in each trimester. (A) First trimester, (B) second trimester and (C) third trimester. The CAS scores were significantly lower in the second trimester ($p = 0.043$); however, no significant differences were observed in the first or third trimester ($p = 0.357$ and 0.273, respectively). The mean CAS scores before and after treatment were 10.0 and 8.0 in the first trimester, 10.0 and 3.0 in the second trimester, and 7.0 and 5.0 in the third trimester, respectively.

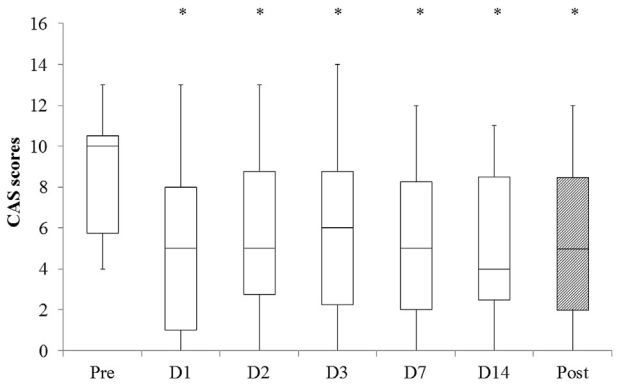

Figure 3. Time course of the constipation assessment scale (CAS) scores. On Day 1 after the initiation of *daikenchuto* therapy, the CAS scores significantly improved ($p = 0.002$). Thereafter, the CAS scores did not significantly differ from those observed on Day 1. The mean CAS score was 10.0 before treatment, 5.0 on Day 1, 5.0 on Day 2, 6.0 on Day 3, 5.0 on Day 7, 4.0 on Day 14, and 5.0 after treatment. * $p < 0.05$ compared with Pre group.

We also examined the safety of *daikenchuto* in pregnant women in this study. In Japan, *daikenchuto* is used in pregnant women in Japan to treat constipation, and is covered by public insurance. According to the animal reproductive toxicology studies, *daikenchuto* has failed to demonstrate a risk to the fetus. Therefore we consider that *daikenchuto* can be regarded as safe for the first trimester of pregnancy. Moreover, *daikenchuto* has been reported to have no effect on either spontaneous contractions or the contractile response of the uterus [17] and is therefore considered to be safe for pregnant patients. In the present study, among the total 20 patients, the incidence of preterm birth and pregnancy-induced hypertension was 10% (2 patients) and 5% (1 patient), respectively. The prevalence of preterm birth and pregnancy-induced hypertension have been reported to be approximately 11% [18] and 7% [19,20], respectively, which are similar to our findings in this study. Furthermore, the clinical courses of both the mothers and fetuses during *daikenchuto* treatment were uneventful in this study. There were no significant effects on the ALT, AST, BUN, or creatinine levels, and no patients exhibited any abnormal values of these parameters. Therefore, we can conclude that there are no significant adverse effects of *daikenchuto* in pregnant women, despite the small number of cases in this analysis.

There are several limitations associated with this study. First, the number of cases was small. A larger study is thus required to overcome this limitation. Second, the CAS, which was employed in the present study to evaluate the symptoms of constipation, consists of a questionnaire, and the results are therefore subjective. However, the diagnosis of constipation is frequently made by the patient, and a *symptom-based diagnosis* of constipation is acceptable for most clinicians. Hence, the CAS method exhibits sufficient evidence of validity and reliability [12] and is potentially useful as a quick assessment tool for evaluating constipation. Third, we have no data regarding food intake and dietary patterns of the patients in this study. Intake of rice and pulses was negatively and that of confectioneries and bread positively associated with functional constipation among a population of young Japanese women [21]. Therefore the further study is required about this issue. Finally, only 25% of cases were nulliparous in this study. To the best of our knowledge, nothing has been reported on whether the parity has an influence on the disease rate of constipation. Further study is necessary about this issue.

In conclusion, this study is the first to assess the efficacy and safety of *daikenchuto* in pregnant women with constipation. Our findings demonstrated that the efficacy of *daikenchuto* therapy is greatest in the second trimester and that a significant effect is achieved the first day after the start of treatment. Although the present data may have some limitations, we hope that our findings will aid in the management of constipation in pregnant women.

Conflicts of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Tytgat GN, Heading RC, Muller-Lissner S, Kamm MA, Scholmerich J, Berstad A, et al. Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting. Aliment Pharmacol Ther 2003;18:291–301.
[2] Horiuchi A, Nakayama Y, Tanaka N. Effect of traditional Japanese medicine, *daikenchuto* (tj-100) in patients with chronic constipation. Gastroenterol Res 2010;3:151–5.
[3] Sato Y, Inoue S, Katagiri F, Itoh H, Takeyama M. Effects of pirensepine on *daikenchuto*-induced elevation of the plasma neuropeptide levels in humans. Biol Pharm Bull 2006;29:166–71.
[4] Ohya T, Usui Y, Arii S, Iwai T, Susumu T. Effect of *dai-kenchu-to* on obstructive bowel disease in children. Am J Chin Med 2003;31:129–35.
[5] Rao SS, Quigley EM, Shiff SJ, Lavins BJ, Kurtz CB, MacDougall JE, et al. Effect of linaclotide on severe abdominal symptoms in patients with irritable bowel syndrome with constipation. Clin Gastroenterol Hepatol 2014;12:616–23.
[6] Iwai N, Kume Y, Kimura O, Ono S, Aoi S, Tsuda T. Effects of herbal medicine *Dai-Kenchu-to* on anorectal function in children with severe constipation. Eur J Pediatr Surg 2007;17:115–8.
[7] Sakakibara R, Odaka T, Lui Z, Uchiyama T, Yamaguchi K, Yamaguchi T, et al. Dietary herb extract *dai-kenchu-to* ameliorates constipation in parkinsonian patients (Parkinson's disease and multiple system atrophy). Mov Disord 2005;20:261–2.
[8] Kono T, Omiya Y, Hira Y, Kaneko A, Chiba S, Suzuki T, et al. *Daikenchuto* (TU-100) ameliorates colon microvascular dysfunction via endogenous adrenomedullin in Crohn's disease rat model. J Gastroenterol 2011;46:1187–96.
[9] Yoshikawa K, Shimada M, Kuwahara T, Hirakawa H, Kurita N, Sato H, et al. Effect of *Kampo* medicine "*Daikenchuto*" on microbiome in the intestine of the rats with fast stress. J Med Invest 2013;60:221–7.
[10] Manabe N, Camilleri M, Rao A, Wong BS, Burton D, Busciglio I, et al. Effect of *daikenchuto* (TU-100) on gastrointestinal and colonic transit in humans. Am J Physiol Gastrointest Liver Physiol 2010;298:G970–5.
[11] Kono T, Koseki T, Chiba S, Ebisawa Y, Chisato N, Iwamoto J, et al. Colonic vascular conductance increased by *Daikenchuto* via calcitonin gene-related peptide and receptor-activity modifying protein 1. J Surg Res 2008;150:78–84.
[12] McMillan SC, Williams FA. Validity and reliability of the Constipation Assessment Scale. Cancer Nurs 1989;12:183–8.
[13] Hanazaki K, Ichikawa K, Munekage M, Kitagawa H, Dabanaka K, Namikawa T. Effect of *Daikenchuto* (TJ-100) on abdominal bloating in hepatectomized patients. World J Gastrointest Surg 2013;5:115–22.
[14] Guarino M, Cheng L, Cicala M, Ripetti V, Biancani P, Behar J. Progesterone receptors and serotonin levels in colon epithelial cells from females with slow transit constipation. Neurogastroenterol Motil 2011;23. 575–e210.
[15] Bradley CS, Kennedy CM, Turcea AM, Ross SS, Nygaard IE. Constipation in pregnancy: prevalence, symptoms, and risk factors. Obstet Gynecol 2007;110:1351–7.
[16] Wald A, Van Thiel DH, Hoechstetter L, Gavaler JS, Egler KM, Verm R, et al. Gastrointestinal transit: the effect of the menstrual cycle. Gastroenterology 1981;80:1497–500.
[17] Murata P, Hayakawa T, Satoh K, Kase Y, Ishige A, Sasaki H. Effects of *Daikenchu-to*, a herbal medicine, on uterine and intestinal motility. Phytother Res 2001;15:302–6.
[18] Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162–72.
[19] Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA 2012;287:3183–6.
[20] Nugteren JJ, Snijder CA, Hofman A, Jaddoe VW, Steegers EA, Burdorf A. Work-related maternal risk factors and the risk of pregnancy induced hypertension and preeclampsia during pregnancy. The Generation R Study. PLoS One 2012;7:e39263.
[21] Murakami K, Sasakii S, Okubo H, Takahashi Y, Hoso Y, Itabashi M, et al. Food intake and functional constipation: a cross-sectional study of 3,835 Japanese women aged 18–20 years. J Nutr Sci Vitaminol (Tokyo) 2007;53:30–6.
[22] Maternal and Child Health Statistics of Japan. Tokyo: Mothers' and Children's Health Organization; 2014. p. 49.