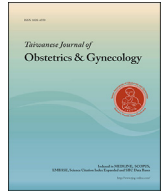




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Original Article

Uses of dietary supplements and herbal medicines during pregnancy in women undergoing assisted reproductive technologies— A study of taiwan birth cohort

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ABSTRACT

Objective: This study aimed to assess the efficacy of dietary supplements and herbal medicines for the care of pregnant women undergoing assisted reproductive technologies (ART).**Materials and methods:** A total of 366 women undergoing ART and their children from the dataset of Taiwan Birth Cohort Study (TBCS, 2005) were enrolled in this study. Structured questionnaires were applied to collect the health information at 6-month follow-up after their delivery. The related use patterns were analyzed to investigate the final birth outcomes.**Results:** Comparing with those of non-ART group, the women undergoing ART consumed more supplements of multivitamin, fish oil, and calcium than herbal medicines during pregnancy. This study revealed that the consumptions of multivitamin, calcium pills, Genseng, and Suz-Wu-Tang were associated with low birth weight, whereas the intake of Huanglian was associated with birth weight. Besides, the uses of multivitamin and Suz-Wu-Tang were related to lower gestational age of infants.**Conclusions:** Physicians and nurses must educate themselves in dietary supplements and herbal/alternative medicines for offering accurate advices for pregnant women to optimize their care. The results could be of reference for further investigation on longitudinal effects of dietary supplements and herbal medicines during pregnancy in women undergoing ART continuously followed with TBCS.© 2018 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The fertility rate in many developed countries and Taiwan has been below replacement level. Also, a dramatic decline in birth rate has become an important issue [1–4]. Infertility is a common condition affecting one out of every six couples during their

lifetime [5,6]. Due to the effect of women's working career during their childbearing period, many infertile couples postponed the birth of their first child beyond the upper limits of female reproductive potential. Assisted reproductive technologies (ART) are the main strategies used to overcome the burden associated with infertility. However, high costs [6–8] and adverse events [9–14] associated with ART can be a huge burden to those infertile couples. As a result, alternative approaches can be considered to prevent potential negative outcomes of mothers and neonates.

Health practices regarding specific dietary prescriptions and restrictions are very common [15–17]. The approaches of prenatal care have been made to decrease pregnancy failure and to increase the health of fetus/baby [18–24]. Chinese herbal medicines (HM) have

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been used as a complementary therapy of female infertility for thousands of years in China, Japan, Korea, and other countries [23]. Herbal medicine use is becoming more popular in pregnant women. However, the safety and efficacy issues should be considered on the recommendation of their health care providers during pregnancy [21,25].

On the other hand, prior studies indicated that micronutrient supplements could have potential benefits on mothers' health, fetal growth, and birth outcomes [22,23,26–28]. The use of micronutrient supplements was associated with higher pregnancy rates not only for women without fertility disorders [29], but also for women with infertility disorders [30–32]. It is very common that pregnant women take various supplements of multivitamins, micronutrients, fish liver oil, fish oil, and calcium micronutrients to maintain a healthy pregnancy [33–36].

This study focused on the final birth outcomes to those mothers who had an infertility history from Taiwan Birth Cohort Study (TBCS) [37]. We aimed to assess the efficacy of dietary supplements and herbal medicines during pregnancy in the care for women undergoing ART.

Materials and methods

Study sample

The TBCS was designed to investigate multiple aspects of newborn/mother pairs with the national birth longitudinal cohort in Taiwan [38]. As a national household probability sampled study, all babies born between October 2003 and January 2004 in Taiwan were eligible for the TBCS with no exclusion criteria. In 2005, 24,200 newborn/mother pairs were enrolled in the TBCS study. Of whom, 21,234 pairs have been continuously followed using standardized and structured questionnaires. A total of 366 mothers with an infertility history undergoing ART was identified for retrospective analyses [37]. This study was reviewed and approved by the Medical Ethics Committee and Data Protection Board in Taiwan before initiated. Informed consent was received for the parents at each data collection period.

Data collection and outcomes

The trained researchers were assigned for home visit and follow-up questionnaire at the 6-month follow-up after giving birth. Participants were asked to report the intake of dietary supplements (including: multivitamin, fish liver oil, fish oil and calcium pills) and herbal medicines during pregnancy period (including: An-Tai-Yin, pearl powder, Huanglian, Szu-Wu-Tang, and ginseng [25,39]). The structured questionnaires offered options for frequency of consumption.

The history of pregnancy, miscarriages, induced abortions, maternal age, spousal factors, educational attainments, household incomes, delivery methods, and pregnancy-related illness were obtained from the TBCS database or the follow-up interviews. Self-reports of female infertility in the current analysis were not confirmed by medical review. The infant information was also collected for analyzing the final birth outcomes such as birth weight and gestational age.

Statistical analyses

Baseline characteristics were reported as the mean \pm standard deviation for continuous variables and as percentages for categorical variables. Student's *t* test was used to compare continuous variables. Chi-square test was used to analyze for categorical variables. Associations between the uses of dietary supplements/herbal medicines and the final birth outcomes were analyzed using Pearson's

correlation. Statistical significances were set at *p* value < 0.05. All statistical analyses were performed with the Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of subjects

Baseline characteristics of infertile women were summarized in Table 1 and the characteristics of their babies were summarized in Table 2. There were 105 (28.7%) women undergoing ART aged over 35 years old (Table 1). As the preliminary findings of TBCS reported [37], ART group (*n* = 366) was 5 years older than non-ART group (*n* = 20868) at the age of delivery (33.2 ± 4.1 v.s. 28.8 ± 4.9 years, respectively; *p* < 0.001). Sixty percent of the participants (*n* = 222) hold an educational attainment of college/university or higher (Table 1). Most of the women undergoing ART were still employed during pregnancy (*n* = 216, 60.7%).

A total of 247 (67.5%) women undergoing ART received Caesarean sections. A total of 95 (26%) women undergoing suffered from severe nausea/vomiting during pregnancy. About one fifth of them were ever hospitalized due to various pregnancy related symptoms. Their mean body weight was 57.3 ± 2.6 kg before pregnancy, and 75.5 ± 3.6 kg prior to delivery, then became 57.3 ± 2.6 kg at 6-month postpartum. There were 63 (17.2%) women reported that they had self-perceived postpartum depression, but only 6 ever sought treatment.

Of the infants whose mothers underwent ART, males were predominant (*n* = 209, 57.1%). A total of 121 (33.1%) infants were with low birth weight (<2500 g), and 154 (42.1%) infants were preterm births (<37 weeks) (Table 2). They had a mean gestational age of 37.1 ± 2.3 weeks (range: 25–41 weeks). Multiple births accounted for 44.3% (*n* = 162). Those born with various genetic birth defects accounted for 9.8% (*n* = 36).

Use patterns of dietary supplements and herbal medicines during pregnancy

As compared with herbal medicine use, there were more women undergoing ART consumed dietary supplements during pregnancy (Tables 3 and 4). A total of 291 (79.5%) women undergoing ART took multivitamin, 85 (23.2%) women took fish oil, and 196 (53.6%) women took calcium pills, 23 (6.3%) women took fish liver oil (Table 3). However, only 50 (13.7%) women took An-Tai-Yin, 50 (13.7%) women took pearl powder, 30 (8.2%) women took Huanglian, 22 (6.0%) women took Ginseng, and 12 (3.6%) women took Szu-Wu-Tang. Most of the women in the ART group consumed less than 10 times herbal medicine use during pregnancy. Supplements of multivitamin, fish oil, and calcium pills were significantly higher in ART group than non-ART group during their pregnancy period of both first trimester and second trimester (all *p* values < 0.001; Table 3). The use of Szu-Wu-Tang was significantly less in women undergoing ART than non-ART group during pregnancy (3.6% vs. 6.3%, *p* values < 0.01; Table 4).

Final birth outcomes under the uses of dietary supplements/herbal medicines among mothers undergoing ART

Table 5 depicts the final birth outcomes for those mothers undergoing ART and various uses of dietary supplements and herbal medicines. The Pearson correlation analysis showed that the use of multivitamin was negatively correlated with gestational age ($r = -0.152$, *p* value < 0.01) and birth weight ($r = -0.177$, *p* value < 0.01). The use of calcium pills was negatively correlated with birth weight of infants ($r = -0.110$, *p* value < 0.05).

Table 1
Characteristics of infertile women undergoing ART.

| Characteristics | Infertile women undergoing ART (N = 366) |
|----------------------------------|--|
| Maternal age at delivery (years) | 33.2 ± 4.1 |
| 20–30 years | 96 (26.2%) |
| 31–35 years | 165 (45.1%) |
| >35 years | 105 (28.7%) |
| Previous pregnancy losses | |
| Spontaneous abortion | 77 (21%) |
| Induced abortion | 59 (12.3%) |
| Stillbirth | 6 (1.6%) |
| Method of delivery | |
| Normal spontaneous delivery | 119 (32.5%) |
| Caesarean section | 247 (67.5%) |
| Educational attainment | |
| High school or less | 144 (39.3%) |
| College/university or higher | 222 (60.7%) |
| Employed during pregnancy | 216 (60.7%) |
| Pregnancy associated illness | |
| Severe nausea/vomiting | 95 (26%) |
| Fever and infectious diseases | 17 (4.6%) |
| Asthma attacks | 4 (1.1%) |
| Gestational diabetes | 23 (6.3%) |
| Pregnancy-induced hypertension | 15 (4.1%) |
| Pre-eclampsia | 6 (1.6%) |
| Hospitalized during pregnancy | 80 (21.9%) |
| Body weight | |
| Pre-pregnancy (kg) | 57.6 ± 2.6 |
| Prior to delivery (kg) | 75.5 ± 3.6 |
| At 6-month postpartum (kg) | 57.3 ± 2.6 |
| Perceived postpartum depression | 63 (17.2%) |

ART: assisted reproductive technologies.

Taking Huanglin was positively correlated with birth weight of infants ($r = 0.112$, $p < 0.05$), whereas Ginseng ($r = -0.121$) and Suz-Wu-Tang ($r = -0.118$) were negatively correlated with birth weight of infants (all p value < 0.05). In addition, the use of Suz-Wu-Tang was negatively correlated with gestational age ($r = -0.113$, p value < 0.05) and birth weight ($r = -0.118$, p value < 0.05).

Discussion

This study indicated that the consumptions of multivitamin, calcium pills, Ginseng, and Suz-Wu-Tang were associated with low

Table 2
Characteristics of infants whose mothers undergoing ART.

| Characteristics | Infants (N = 366) |
|---|-------------------|
| Male gender | 209 (57.1%) |
| Gestational age (weeks) | 37.1 ± 2.3 |
| <37 weeks | 154 (42.1%) |
| Birth weight (g) | 2749 ± 598 |
| <2500 g | 121 (33.1%) |
| Birth number | |
| Singleton | 204 (55.7%) |
| Multiple | 162 (44.3%) |
| Perceived general health conditions of babies | |
| Very good | 185 (50.5%) |
| Good | 122 (33.3%) |
| Fair | 57 (15.6%) |
| Not good | 2 (0.5%) |
| Genetic birth defects | 36 (9.8%) |
| Nervous system | 4 (1.1%) |
| Facial system | 6 (1.6%) |
| Cardiovascular system | 11 (3%) |
| Digestive system | 3 (0.8%) |
| Urogenital system | 7 (1.9%) |
| Musculoskeletal system | 6 (1.6%) |
| Respiratory system | 1 (0.3%) |
| Chromosomal abnormalities | 1 (0.3%) |
| Others | 9 (2.5%) |

birth weight, whereas the intake of Huanglin was positively associated with birth weight. Besides, the uses of multivitamin and Suz-Wu-Tang were related to lower gestational age of infants. The significantly higher uses in multivitamin, fish oil, and calcium pills among the women undergoing ART were noted in this study. These findings suggest that nutrition intake via dietary supplements attracting increased interest during pregnancy among the mothers with previous infertile experience. Furthermore, those women undergoing ART might feel more confident to take dietary supplements than herbal medicines, except fish liver oil. Although prior study showed that fish liver oil may have beneficial impacts on pregnant women [40], possible contaminants (such as polychlorinated biphenyls and mercury) in commercial products of fish liver oil could be a concern for those pregnant women.

A higher proportion of ART pregnancies were associated with obstetrical and perinatal complications, and that children conceived through ART may have a higher risk of abnormalities or preterm delivery than spontaneously conceived children [41–43]. According to a systematic review, better cognitive and/or psychomotor outcomes were reported for supplementations involving multiple micronutrients and n-3 fatty acid. In contrast, null results of pregnant women on child neurodevelopment were observed while giving single micronutrient supplementation, such as iron, folic acid, vitamin A, and zinc [34,44]. Since multivitamin use was associated with higher pregnancy rates for both infertile women and those without infertile disorders, the use of multivitamin may be higher among women planning a pregnancy [29–32]. In the present study, those pregnant women after receiving ART were more likely to take multivitamin than required. More interesting is that the intake of multivitamin was negatively correlated with gestational age and birth weight of infants. However, we were not able to draw a conclusion.

Previous studies indicated calcium supplements were associated with lower risk of preterm birth or serious morbidities [33,45]. Consumption of fish liver oil that contains high levels of vitamins A and D has been shown to have a positive effect on the infant size at birth [40]. There are also epidemiologic evidences that fish oil (a rich source of long-chain omega-3 fatty acids) was associated with mental development of children and improvement of infant size [35,40,46]. Our study results are not identical with prior studies.

Regarding the intake of herbal medicine during pregnancy, our study findings indicated that the consumptions of Ginseng and Suz-Wu-Tang were associated with lower birth weight and gestational age of infants. The results were contrary to users' expectations and beyond our ability to reach a conclusion. Ginseng and Suz-Wu-Tang are very common used herbal medicines among Chinese women. While the use of these herbal medicines is believed to be prevalent, little is known about their mechanism specifically during pregnancy. The participants might have been using other natural products or/and medications in addition to those herbal medicines and dietary supplements, which lead to concerns about possible adverse interactions [47].

Although many consumers assume that herbal medicines are safe and effective, evaluations of many herbal medicines of defined formulas by well-designed clinical trials or appropriate animal studies are still in luck [48–50]. For example, the compositions of herbs in Sheng-Hua-Tang and Szu-Wu-Tang are different in China and Taiwan, their proportions are not even precisely described [25,51]. Despite these herbal medicines have a long history of use in treating gynaecological disorders among Chinese women [23,51,52], those herbal formulas are not regulated to the same degree as traditional pharmaceutical products and the quality of their raw materials can vary from batch to batch. It is important to monitor their use, particularly in the case of pregnancy. In the absence of evidences, knowledge of herbal medicine uses is

Table 3
Consumption of dietary supplements during pregnancy among women undergoing ART and spontaneous conception (Non-ART).

| Dietary supplements | ART (n = 366) | Non-ART (n = 20868) | Pregnancy stages | | | |
|---------------------|---------------|---------------------|------------------|--------------|------------------|---------------|
| | | | First trimester | | Second trimester | |
| | | | ART | Non-ART | ART | Non-ART |
| Multivitamin | 291 (79.5%)* | 12231 (58.6%) | 126 (34.4%)* | 4436 (21.3%) | 283 (77.3%)* | 11829 (56.7%) |
| Fish liver oil | 23 (6.3%) | 1507 (7.2%) | 10 (2.7%) | 554 (2.7%) | 22 (6%) | 1387 (6.6%) |
| Fish oil | 85 (23.2%)* | 3297 (15.8%) | 27 (7.4%)* | 1093 (5.2%) | 83 (22.7%)* | 3210 (15.4%) |
| Calcium pills | 196 (53.6%)* | 8567 (41.1%) | 85 (23.3%)* | 1035 (5.0%) | 85 (23.3%)* | 3208 (15.4%) |

ART: assisted reproductive technologies.

* $p < 0.001$, ART vs. non-ART.

Table 4
Consumption of herbal medicines during pregnancy among the women undergoing ART and spontaneous conception (Non-ART).

| Herbal Medicines | Intake during pregnancy | | Frequency (times) | | | | |
|------------------|-------------------------|---------------------|-------------------|---------|----------|---------|----------|
| | ART (n = 366) | Non-ART (n = 20868) | 1–10 | 11–20 | 20–40 | 40–60 | ≥61 |
| An-Tai-Yin | 50 (13.7%) | 2817 (13.5%) | 37 (10.1) | 5 (1.4) | 4 (1.1) | 1 (0.3) | 3 (0.8) |
| Pearl powder | 50 (13.7%) | 2483 (11.9%) | 10 (2.7) | 9 (2.5) | 10 (2.7) | 4 (1.1) | 17 (4.6) |
| Huanglian | 30 (8.2%) | 2212 (10.6%) | 8 (2.2) | 7 (1.9) | 5 (1.4) | 4 (1.1) | 6 (1.6) |
| Ginseng | 22 (6%) | 939 (4.5%) | 14 (3.8) | 0 (0.0) | 3 (0.8) | 2 (0.5) | 3 (0.8) |
| Suz-Wu-Tang | 13 (3.6%)* | 1315 (6.3%) | 11 (3.0) | 1 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.3) |

ART: assisted reproductive technologies.

* $p < 0.01$ when compared to non-ART group.

Table 5
The correlation coefficient between the consumptions of dietary supplements/ herbal medicines and the birth outcomes during pregnancy (N = 366).

| | Gestational age | Birth weight |
|---------------------|-----------------|--------------|
| Dietary supplements | | |
| Multivitamin | -0.152** | -0.177** |
| Fish liver oil | 0.002 | 0.022 |
| Fish oil | 0.005 | -0.005 |
| Calcium pills | -0.063 | -0.110* |
| Herbal medicines | | |
| An-Tai-Yin | -0.022 | -0.026 |
| Pearl powder | 0.022 | 0.046 |
| Huanglian | 0.084 | 0.112* |
| Ginseng | -0.076 | -0.121** |
| Suz-Wu-Tang | -0.113* | -0.118* |

* $p < 0.05$; ** $p < 0.01$.

particularly important. Even small risks might well outweigh benefits [50].

The advantage of this study was performed with a large scale national longitudinal study (TBCS) with very high response rate. The results were of both great representation of practices during pregnancy of ART subjects and implications for further actions. The disadvantages of this study included obsolete data collected in 2000s. However the data could be served as baseline data for further investigation on the longitudinal effects of dietary supplements and herbal medicines in the future study to remedy this shortage on this important area. It is important to emphasize that there were some limitations while interpreting the data pertaining to dietary supplements or herbal medicine consumptions collected through recalls or questionnaires that conducted at 6 months after giving birth. In a study such as this, where the uses of dietary supplements and herbal medicines were collected retrospectively, the accuracy of reported exposures remains a concern. In addition, the roles of diets, healthy habits, lifestyles were unclear, and no blood tests or medical record review was assessed. Furthermore, many confounding factors existed in this study, these relationships and interpretations need further study and clarification.

Conclusions

Despite these limitations, it is clear that physicians and nursing staffs must educate themselves in the field of dietary supplements and herbal/alternative medicines in order to offer accurate advices for pregnant women to optimize their care. It is important for obstetrician gynecologists to note that many herbal medicines are still not subject to standardized manufacturing or regulation by the authorities of Taiwan. Thus, variations in therapy and safety can be still a prominent issue. Physicians must be cautious for the safety of dietary supplements and herbal medicine intake. The results of this study could be of reference for further investigation on longitudinal effects of dietary supplements and herbal medicines during pregnancy in women undergoing assisted reproductive technologies continuously followed with TBCS.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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