Knowledge of Iatrogenic Premature Ovarian Insufficiency Among Chinese Obstetricians and Gynecologists: A National Questionnaire Survey

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Research

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Abstract

Background: With increasing cases of iatrogenic premature ovarian insufficiency (POI), more clinicians are required to counsel patients regarding the gonadotoxic effects of iatrogenic treatments. This survey aims to explore obstetricians and gynecologists' knowledge regarding iatrogenic POI. A national online questionnaire survey was conducted across China. Respondents were asked to select the iatrogenic condition(s) that can cause POI based on their experience and knowledge.

Results: Of the 5,523 returned questionnaires, 4,995 were analyzed. Among tumor therapies causing POI, most respondents agreed that radiotherapy (73.5% of respondents) and chemotherapy (64.1%) are risk factors for POI. While only 6.5% and 7.8% of the gynecological oncologists believed tumor immunotherapy and tumor-targeting therapy, respectively, may cause ovarian impairment, 31.8% and 22.2% of the non-gynecologic oncologists believed that these therapies could affect ovarian health. Most respondents believed that ovarian cystectomy (54.4%) was a risk factor for POI, while only a few respondents believed that hysterectomy with bilateral salpingectomy (39.6%) and uterine artery embolization (33.5%) could cause ovarian impairment. Only 30.5% respondents believed that immunosuppressants increased the risk of POI. Views differed with experience and hospital setting.

Conclusions: The knowledge of gonadal toxicity due to traditional tumor treatments is generally high among Chinese obstetricians and gynecologists. A misunderstanding may exist in primary care hospitals and general gynecologists regarding a link between novel tumor treatments and POI, owing to the lack of convincing evidence. Knowledge of POI caused by hysterectomy and immunosuppressants should be improved.

Background

Premature ovarian insufficiency (POI) is a clinical syndrome defined by loss of ovarian activity before the age of 40 years [1].The incidence of spontaneous POI, typically assumed to occur in approximately 1% of adult women [2], has increased to 2.4–2.8% in recent years [3, 4]. As a consequence of being exposed to lower estrogen for a longer period, women with POI have an increased risk of premature morbidity and mortality [5], cardiovascular and cerebrovascular diseases [6, 7], osteoporosis [8, 9], impaired cognition [10], and diminished sexual health [11]. However, the etiologies of POI are largely unknown. Of the few identified causes, iatrogenic conditions account for a large proportion (~ 65%) of cases [12], including radiotherapy (RT), chemotherapy (CT), and drugs for various autoimmune diseases [13, 14]. The incidence of iatrogenic POI has been reported to be growing owing to increasing survival rates following diverse cancer treatments [15–17]. In addition, accumulating evidence has revealed that women with endometriosis or a history of pelvic surgery are more likely to have severely compromised ovarian function, including POI [18, 19]. Taken together, the increasing prevalence of iatrogenic POI has posed great challenges to clinicians, especially obstetricians and gynecologists.

Fortunately, iatrogenic POI can be partially avoided or reduced using many preventative measures, including optimization of CT regimens or radiation field, application of gonadotropin-releasing hormone agonist (GnRH-a), and fertility-sparing surgical strategies, all of which are implemented by physicians. It has been continually emphasized that proper and comprehensive fertility counseling should be provided to patients who are within their reproductive ages prior to starting iatrogenic treatment so that they are informed on both the risk of treatment-related gonadotoxicity and the potential future needs of accessing an assisted reproductive clinic. To this end, the knowledge of iatrogenic POI among clinicians is particularly important. Therefore, we surveyed obstetricians and gynecologists across China about their general knowledge of iatrogenic POI to fully investigate the current understanding of this condition and any underlying challenges in this population.

Results

General background information of respondents

Of the 5,524 questionnaires that were returned, 249 were answered by respondents who were neither obstetricians nor gynecologists and were excluded, leaving a qualified sample of 4,995 (95.5%). General background information about the respondents is presented in Table 1. Most respondents were women (96.2%), aged 36–55 years (69.2%), with over 10 years of working experience. In terms of respondents' work setting, 34.9% of respondents worked in tertiary hospitals and 49.0% in secondary hospitals. Meanwhile, 51.5% of respondents practice at general hospitals and 42.9% practice at maternity and children hospitals, or reproductive hospitals. Most participants (79.5%) specialized in gynecology, including reproductive endocrinologists, obstetricians-gynecologists (who work as a gynecologist and an obstetrician simultaneously), and gynecologists.

Table 1
General background information about the respondents.

Category	N (%)
Gender	
Female	4805 (96.2)
Male	190 (3.8)
Age in years	
18–25	112 (2.2)
26–35	1079 (21.6)
36–45	2065 (41.3)
46–55	1529 (30.6)
>55	210 (4.2)
Length of service (years)	
≤5	677 (13.6)
6 ~ 10	861 (17.2)
11 ~ 20	1517 (30.4)
>20	1940 (38.8)
Hospital level	
Tertiary hospital	1745 (34.9)
Secondary hospital	2445 (49.0)
Community hospital or others	448 (16.1)
Hospital type	
General hospital	2572 (51.5)
Maternity and child care hospital	2144 (42.9)
Others	279 (5.6)
Specialty type	
General gynecologist	3400 (68.1)
Gynecologic or reproductive endocrinologist	345 (6.9)
Obstetrician-gynecologist	147 (2.9)
Gynecologic oncologist	77 (1.54)

Category	N (%)
Obstetrician	1026 (20.5)
Total	4995 (100)

Iatrogenic condition(s) to induce POI

A summary of Chinese obstetricians and gynecologists' views on iatrogenic condition(s) that can induce POI is presented in Table 2. Among the tumor therapies respondents thought would induce POI, RT ranked first (73.5%), followed by CT (64.1%), tumor immunotherapy (TIT) (31.8%), and tumor-targeting therapy (TTT; 22.2%) ($p < 0.05$).

Table 2
Chinese obstetricians and gynecologists' views on iatrogenic condition(s) to induce POI.

Variable	N (%)	χ^2	p
Tumor therapies			
Radiotherapy	3669 (73.5)	1459.1	< 0.01
Chemotherapy	3202 (64.1)		
Tumor immunotherapy	1590 (31.8)		
Tumor-targeting therapy	1109 (22.2)		
Surgeries or procedures			
Ovarian cystectomy	2716 (54.4)	1288.4	< 0.01
Hysterectomy with bilateral salpingectomy	1980 (39.6)		
Uterine artery embolization	1675 (33.5)		
Bilateral salpingectomy	1246 (24.9)		
Bilateral tubal ligation	779 (15.6)		
Others			
Immunosuppressant	1523 (30.5)	/	/

Most respondents believed that ovarian cystectomy (OC) could have an adverse impact on ovarian reserve (54.4% of respondents), whereas a minority believed that hysterectomy with bilateral salpingectomy (H&BS; 39.6%), uterine artery embolization (UAE; 33.5%), bilateral salpingectomy (BS; 24.9%), or bilateral tubal ligation (BTL; 15.6%, $P < 0.05$) could have an adverse impact on ovarian reserve. Only 30.5% respondents believed that immunosuppressants (IS) could lead to an increased risk of POI.

Influencing factors

Analysis demonstrated that the level of understanding about the risk of POI with different treatments varied with length of service and hospital setting. A visualization of the correspondence analysis is shown in Fig. 1. For example, respondents with over 20 years of service were more likely to consider RT, BS, and H&BS as risk factors for POI than those in other age groups. Meanwhile, those with less than 5 years of service typically only indicated the risk of POI caused by OC. Physicians from tertiary hospitals might pay more attention to ovarian impairment caused by UAE, while those from secondary hospitals were more aware of the link between the ovarian impairment and CT and BTL. Interestingly, TTT, TIT, and IS were considered more often to be risk factors for POI by physicians from community hospital or others, where advanced treatments are less likely to be available. Finally, while 6.5% and 7.8% of the gynecological oncologists believed that TIT and TTT may adversely affect the ovarian reserve, respectfully, 31.8% and 22.2% of non-gynecologic oncologists believed that the same treatment may be a risk factor for POI.

Discussion

Tumor therapy

In women, primordial germ cells (PGCs) enter meiosis at week 10, progressing to prophase I and remaining at this stage for a long period until ovulation [20]. This process makes PGCs extremely sensitive to the effects of CT and RT. Evidence suggests that the incidence of POI in female survivors of childhood and adolescent cancer is 2.1– 82.2% [21]. RT can be more damaging to ovarian tissue than CT because apart from being particularly irreversibly toxic to oocytes [22, 23], its off-target effects can also affect the surrounding tissue [24]. A rapidly growing group of cancer survivors requires availability of more physicians to better counsel patients regarding the gonadotoxic effects of cancer treatment and provide them with appropriate options. However, a recent study in 2014 demonstrated that while 71% of oncologists were aware of the risk of POI following exposure to alkylating agents, only 15% of primary care physicians were aware of this risk [25]. This nationally representative study found that there is some general knowledge about tumor-treatment-related POI among Chinese obstetricians and gynecologists. Among respondents, 73.5% and 64.1% were aware that RT and CT, respectively, are the two main factors leading to the decline of ovarian reserve. Furthermore, respondents with more than 10 years of experience working in secondary or tertiary hospitals had better knowledge regarding risk factors for iatrogenic POI than others. Therefore, relevant fertility-related education should be provided in a more targeted manner in the future.

Recently, novel therapies including TTT and TIT have been increasingly used in clinical settings. Despite their high selectivity, they may also affect healthy cells and tissues, including gonadal tissues, as highlighted by animal studies [26]. Unlike the direct toxicity of RT or CT, TTT tends to influence folliculogenesis, PGC establishment, or ovarian follicular growth and differentiation by acting on the corresponding signaling pathways [26]. However, available human data on the association between TTT and ovarian health are limited and heterogeneous [27]. Most existing data are from retrospective evaluations [28] or case reports [29]. For instance, Allegra et al [28] reported that new-onset POI occurred

in 39% of patients treated with the combination of modified FOLFOX-6 and bevacizumab (a type of TTT) compared with 2.6% in the control group treated with modified FOLFOX-6. In this cohort, ovarian function recovered in 86% of patients after cessation of treatment. Regarding TIT, existing data are more limited, but experts in this field are optimistic about its efficacy [30]. The results of our survey demonstrated that most physicians from community hospitals or others tended to believe TIT and TTT may cause adverse effects to ovarian reserve, which, however, was not the case for most gynecological oncologists. These phenomena imply that the popularization and speed at which relevant information is updated among physicians practicing at different level hospitals and specialties vary considerably. With a lack of convincing public data, the chances are slim that primary care physicians will be aware of the risks of novel therapies to ovarian health without continually reviewing the literature. Therefore, to improve the reproductive health and long-term quality of life of cancer patients, both well-designed clinical observations and more accessible information and education for clinicians are required.

Surgeries or procedures

POI induced by non-oophorectomized surgeries is less common than traditional cancer treatment, but since these surgeries are regular treatment for many benign gynecological conditions or early tumors at any age, their impact on fertility should not be ignored. Evidence has confirmed that OC has been associated with a reduction in ovarian reserve, especially in patients with severe endometriosis [31–33]. Our survey demonstrated that OC-inducing ovarian impairment was commonly known among respondents, even in those with less than 5 years of service. This indicates that POI caused by OC may not be uncommon in clinical practice.

Anatomically, H&BS, UAE, BS, and BTL may reduce blood supply to the ovaries to varying degrees, thus having a potential impact on ovarian reserve. Previous studies have demonstrated a certain reduction in ovarian function after H&BS [34, 35]. In 2011, Moorman et al. published their prospective research including 2,410 patients aged between 30 and 47 years, revealing a nearly two-fold increased risk for ovarian failure among women undergoing hysterectomy without bilateral oophorectomy compared with women of similar age with intact uteri (level of evidence: II) [36]. With accelerating menopause and hormone deprivation caused by hysterectomy, an increased overall risk of morbidity and mortality is also revealed. A cohort study of 666,588 women demonstrated that hysterectomy without oophorectomy performed before age 35 and H&BS performed before age 45 were associated with an increase in all-cause mortality (hazard ratio, 1.29 and 1.15, respectively) [37] and the incidence of depression [38]. However, in our study, only 39.6% of the obstetricians and gynecologist respondents were aware of H&BS causing diminished ovarian reserve. From a public health perspective, these are vital issues that require further training and education for health professionals to avoid unnecessary hysterectomy.

Women under age 40 appear not to be affected by UAE [39]. Out of 7.3% of cases of amenorrhea after UAE, 86% occurred in patients 45 years or older [40]. While a meta-analysis of 353 patients demonstrated that UAE may not result in impaired ovarian reserve, regardless of age [41], other studies with small sample sizes demonstrated the opposite result [42, 43]. Our survey demonstrated that 33.5% of respondents still worried about UAE leading to POI, especially in tertiary hospitals where UAE procedures

are completed more frequently. BS and BTL are less likely to induce POI, as they may have no short-term significant effects on ovarian function indicators [44–46]. However, their long-term effect on fertility outcomes remains uncertain [44, 47]. Most respondents remained optimistic about the effects of BS and BTL on ovarian health.

Immunosuppressants

ISs are often used for long-term treatment of autoimmune diseases, such as systemic lupus erythematosus (SLE), which predominantly affect young women. Some of these agents have distinctive gonadal toxicity. For example, cyclophosphamide has been considered as an independent risk factor of POI in SLE patients [13]. During the administration of cyclophosphamide, the incidence of POI was < 50% of women under age 30 and 60% of women between ages 30 and 40 [48]. Reversible amenorrhea (64.3% of patients) [49] and irregular menstruation (70% of patients) [50] were also observed in premenopausal women following exposure to *Tripterygium wilfordii* Hook.f., a well-known Chinese herbal medicine with an immunosuppressive effect. However, 69.5% of respondents to our survey were not aware of the gonadal impairment of IS, which appeared more prevalent among respondents from tertiary hospitals. As IS agents are typically prescribed by an immunologist or an internal medicine physician, we speculate that these differences may be due to a high degree of departmental specialization in tertiary hospitals. Thus, it is necessary to conduct relevant training and education and strengthen the exchange of experience between different departments on IS use.

Conclusions

This national survey is the first to explore obstetricians and gynecologists' knowledge and awareness regarding iatrogenic POI. Taking respondents' background information into consideration, the results of this survey not only generate a clearer picture of the understanding of iatrogenic POI in this field, but also help us determine the underlying problems in knowledge translation. However, there were some limitations: the proportion of respondents with different backgrounds (gender, specialty, or hospital type) was unevenly distributed; the iatrogenic measures listed in the questionnaire were limited and we did not give a detailed explanation for the immunosuppressants included in the survey. Therefore, further investigations and improved survey design are needed to confirm and update our conclusions. Our survey demonstrated that the knowledge of gonadal toxicity of traditional tumor treatments is generally high among obstetricians and gynecologists, but there is still a relative lack of understanding among physicians with less experience and/or from community hospitals. A misunderstanding may exist in community hospitals and among non-gynecologic oncologists relating novel tumor treatments and ovarian health due to the lack of convincing evidence. Additionally, the knowledge of POI caused by hysterectomy and IS agents needs to be improved. Based on these results, we hope to carry out more purposeful and targeted doctor re-training in the future.

Methods

Study setting and implementation

An online survey was administered to obstetricians and gynecologists across China between June 7 and July 3, 2020. The questionnaire was distributed with the assistance of the China Maternal and Child Health Association, Society of Gynecological Endocrinology and answered anonymously. The study was reviewed and approved by the Ethics Committee of Peking Union Medical College Hospital (Ethical code number: S-k1189-1; date of approval: May 08, 2020) and is in accordance with the Declaration of Helsinki.

Questionnaire design

The questionnaire included the following sections: (1) general background information of the respondent; (2) Tumor therapies and POI; (3) Surgeries or procedures and POI; and (4) Immunosuppressants and POI. There were 16 questions in total, and full questionnaire details are provided in Supplementary material.

Statistical analysis

Data analysis was performed using SPSS (ver. 25.0 IBM, Armonk, NY, USA). Categorical variables are presented as a number (frequency) and percentage. The association between two categorical variables was tested using the chi-square test. Due to the large variation in the sample size among subgroups, subgroup analyses were not performed based on physicians' gender, specialty, or hospital type. An overlap existed among respondents regarding age and length of service, with the latter being more representative of work experience. Thus, subgroup analyses were conducted based on physicians' length of service and hospital type (community, secondary, and tertiary). Statistically significant associations were defined as having $P < 0.05$. To better understand the discriminative variables, a correspondence analysis was conducted to visualize the correlation among variables.

List Of Abbreviations

BS Bilateral salpingectomy

BTL Bilateral tubal ligation

CH Community hospital

CT Chemotherapy

GnRH-a Gonadotropin-releasing hormone agonist

H&BS Hysterectomy with bilateral salpingectomy

IS Immunosuppressants

OC Ovarian cystectomy

PGC Primordial germ cells

POI Premature ovarian insufficiency

RT Radiotherapy

SLE Systemic lupus erythematosus

TIT Tumor immunotherapy

TTT Tumor-targeting therapy

UAE Uterine artery embolization

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics Committee of Peking Union Medical College Hospital (Ethical code number: S-k1189-1; date of approval: May 08, 2020).

Consent for publication

Not applicable.

Availability of data and materials

Data and materials are summarized in the manuscript, figures, and tables.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

YFW and AJS implemented the research plan and were responsible for the questionnaire design. YFW, YZ, and AJS oversaw the formal analysis, conceptualization and writing of the manuscript. WW, QZ, YF, YZ, HD, ZYT, XQZ, YQZ, DHP, and XMY provided valuable comments and suggestions on the questionnaire revision and played a critical role in the distribution, completion, and collection of questionnaires. AJS and YZ provided a critical contribution to the organization and cooperation of this arduous task

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Figures

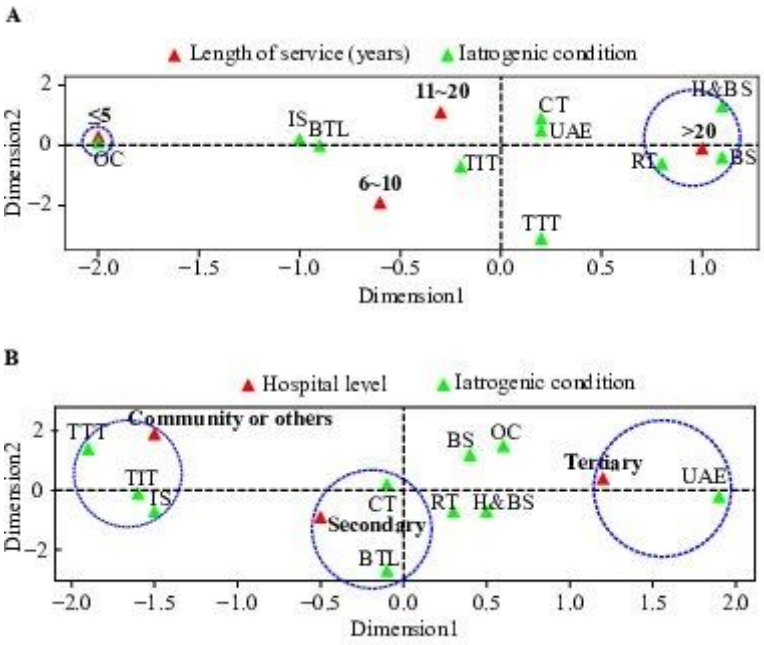

Figure 1

Visualization of the correspondence analysis by physician's length of service (A), and level of hospital (B). The interpretation rate in each dimension is: 87.7% (Dimension 1) and 7.50% (Dimension 2) in A; and 98.9% (Dimension 1), 1.1% (Dimension 2) in B. More details are available in Supplementary Table 1 and Supplementary Table 2. Abbreviations: RT: radiotherapy; CT: chemotherapy; TIT: tumor immunotherapy; TTT: tumor-targeting therapy; OC: ovarian cystectomy; H&BS: hysterectomy with bilateral salpingectomy; UAE: uterine artery embolization; BS: bilateral salpingectomy; BTL: bilateral tubal ligation; IS: immunosuppressant.

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