

Patterns of pediatric and adolescent gynecological problems in China: A hospital-based retrospective study of 97,252 patients and a systematic review

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Abstract

Objective: To describe the pattern and population characteristics of pediatric and adolescent gynecological (PAG) problems in China. **Design:** A clinic-based retrospective study of gynecological patients (aged 0-18 years) over a period of 13 years, and a systematic review of related studies in China. **Setting:** Department of PAG at The Children's Hospital of Zhejiang University School of Medicine. **Population or Sample:** The final analyses included 97,252 patients with gynecological problems. **Methods:** Descriptive analysis was conducted to evaluate the pattern of PAG problems. The weighted average of PAG problem percentages were calculated. **Main Outcome Measures:** Spectrum of PAG problems **Results:** The number of first-visit PAG patients increased from 4,582 to 11,876 from 2006 to 2018. Overall, genital inflammation was the most common presentation (57.0%), followed by early puberty (18.2%). The disease pattern varied across age groups, the most common problems were genital inflammation for age 0-6 years; genital inflammation and early puberty for age 7-9 years; consultation of growth and development, genital inflammation and menstrual disorder for age 10-18 years. Summarizing twenty previous studies of outpatient PAG patterns in China, we found an average weighted percentage of 48.8% for genital inflammation and 25.2% for menstrual disorder. **Conclusion:** Genital inflammation, early puberty, consultation of growth and development and menstrual disorder were common issue for pediatric and adolescent patients with gynecological problems in China. **Funding** The National Nature Science Foundation of Zhejiang (LQ18H040001, LY20H040011) Medical Scientific Projects from Health department of Zhejiang Province(2017KY101) **Keywords:** Pediatric and adolescent gynecological; disease patterns; retrospective study; systematic review

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Introduction

Childhood and adolescence are critical periods for reproductive development and long-term health maintenance. Some gynecological problems resulting from inappropriate advice and care and mishandling in adult clinics can have a significant impact on the reproductive, physical and mental health of patients that can last years, even into adulthood.^{1,2} They might therefore place a heavy economic burden on patients, families and society.

Pediatric and Adolescent Gynecology (PAG) is a subspecialty under the umbrella of Obstetrics and Gynecology that focuses on the diagnosis and medical and surgical management of female reproductive health problems from birth through young adulthood. It requires a multidisciplinary approach and involves a range of female reproductive healthcare services, from first gynecologic visits to specialized care for congenital conditions and other reproductive disorders.³ PAG in western countries such as the U.S., Europe, and Australia^{1,4,5} have established for some decades and continue to focus on caring the gynecological and reproductive health of female children and adolescents. Even in these more advanced settings, studies have reported a substantially unmet need for specific health concerns among children and adolescents.^{1,6} The need is even greater in resource-poor and developing settings. Despite the deemed significance of the problem, very few large-scale studies, looking at the problem in a granular and robust way, exist to elucidate the pattern and characteristics of PAG problems worldwide, especially in developing countries. Currently, there are few hospitals in China equipped with a specialized PAG department. One of these is the children's hospital of Zhejiang University School of Medicine (ZJU), and it has carried out clinical gynecological work for children and adolescents for nearly 20 years, providing clinical outpatient services to more than 100,000 patients thus far. Because of the department's longstanding efforts in this area, it is in a unique position to evaluate the patterns of PAG problems over time in China. This retrospective study analyzed 13 years of the hospital's patient data and aimed to describe the pattern, distribution characteristics, and trends in PAG problems over time. Additionally, we conducted a systematic review focused on previous studies examining PAG problems in China.

Methods

Study design

Based on the hospital outpatient service system, we reviewed all electronic medical record (EMR) of outpatients treated in the Pediatric and Adolescent Gynecology (PAG) Department in the Children's Hospital, Zhejiang University School of Medicine from January 2006 to December 2018. The study was approved by the Human Subjects Committees of the Children's Hospital, Zhejiang University School of Medicine.

Study population

The primary inclusion criterion for the study was outpatients at the ZJU PAG clinic who were under the age of 18 between 2005 and 2018. Among 207,287 patients with information on the primary diagnosis at first clinical presentation, 110,035 patients were excluded because they were diagnosed with urologic or other non-gynecological diseases or conditions. The final analysis included 97, 252 patients.

Assessment of PAG problems

Outpatient record information including patient number, name, age, date of birth, telephone number, address, date of visit, diagnoses and the patient category (first visit or subsequent visit) were recorded and analyzed. All EMR information was extracted by one individual. Then the data was independently reviewed by a second individual and a third individual if necessary. Extensive assessment depending on first visit

and further consultation data, first diagnosis, second diagnosis, third diagnosis, referral information, symptoms, admission to hospital, treatment and follow-up situation were carried out by descriptive analysis and interference analysis.

In the study, PAG problems were assessed based on the first diagnosis among patients at their first clinical visit. Referring to the ICD-10 code for adult gynecology, all newly diagnosed patients were selected as new data and divided into ten major categories: genital inflammation (including vulva and vaginal abscess, vulvitis, vulvovaginitis, lichen sclerosus, labia adhesion, foreign body in vagina), early puberty (including skeptical precocity, peripheral precocious puberty, central precocious puberty), consultation of growth and development, gynecological examination, menstrual disorder (including abnormal uterine bleeding-ovulatory dysfunction (AUB-O), amenorrhea, ovarian failure, dysmenorrhea, metabolic syndrome and polycystic ovary syndrome), other endocrine problems (including abnormal development of breast and accessory breast, growth retardation and dwarfism, hypothalamic-pituitary lesion, congenital adrenal hyperplasia, sexual dysplasia), genital trauma (including trauma from accident or fall, etc.), masturbation syndrome, anomalies of the genital tract (including hymen atresia, excessive hymen, vaginal atresia, oblique vaginal septum syndrome, Mayer-Rokitansky- Küster-Hauser syndrome and so on) and ovary and genital tumor (including ovarian neoplasms, postmenopausal osteoporosis and vaginal neoplasms).

Covariates

Information on covariates of interest, including date of diagnosis, date of birth and residency, was extracted from the patients' EMR. Age was calculated based on the time interval between date of birth and date of diagnosis.

Systematic review

We carried out a systematic review and meta-analysis in order to understand how our findings relate to the broader context of studies previously published in China. We searched the China National Knowledge Internet (CNKI), Wanfang (Chinese), Web of Science and Pubmed databases without restriction for publication date and languages on January 13th, 2021. The following terms were used to achieve specific searches: 'pediatric gynecology', 'adolescent gynecology', 'pediatric and adolescent gynecology', 'girls', 'China' and 'Chinese'. We retrieved additional studies by surveying references of other reports and by using the MEDLINE option 'Related Articles.'

The initial search strategy yielded 1235 articles, of which 1198 were excluded after a review of the title and abstract. The articles involved with the disease spectrum analysis of children and teenagers' gynecological outpatient records were included; those of full text cannot be found, having no disease spectrum data, duplicate publication or identical data, pathological analysis, and case report were excluded. None of the articles found through Pubmed and Web of Science databases met the inclusion criteria. Thirty-seven articles from CNKI and Wanfang met the necessary requirements for the study and were fully read. Of these, four articles were excluded because of overlapping data or weak study designs. Two investigators conducted the search and identified eligible studies independently. In total, 33 studies (20 outpatient and 13 inpatient studies) were included in our systematic review (Table S1). Notably, all of the included studies were originally published in Chinese journals.

Statistical analyses

Descriptive analysis was conducted to evaluate the pattern of PAG problems overall and by age, year, and region. The differences in those patterns across age, year and region were evaluated using χ^2 test of proportions. All analyses were conducted using SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

The meta-analysis was conducted with Stata 16.0 (Stata Corp, College Station, TX, USA). For each study in the systematic review, we calculated the weighted average percentage of each article that met our inclusion criteria by taking disease species as subgroup. Because not all of the articles included in the meta-analysis had all disease classifications, the disease proportion was weighted to 100% for final analysis. By using the I^2 statistic to assess heterogeneity between studies, summarized effect size (ES) (95% CI) was derived.

Results

Basic characteristics of the study population

Over 13 years, a total of 97, 252 patients visited the PAG department, and the total number of visits was 206,967. During the study period, the number of PAG patients that came in for a first visit increased gradually from 4,582 in 2006 to 11,876 in 2018 (Figure 1). Table 1 shows the characteristics of patients at first visit during the study period. The figures below ‘Follow-up times’ in the table refer to the number of patient visits. Patient ages ranged from 0 to 18 with a mean \pm standard deviation (SD) of 6.3 ± 3.9 years; 51.7% of the participants were aged 0-6 years, 27.2% were aged 7-9 years, and 21.0% were aged 10-18 years. Over 94% of patients were from Zhejiang province; over half (55.2%) of the patients was from Hangzhou city, where the hospital is located. The average number of appointments per subsequent visited patient was 3.7.

PAG patterns overall and by age groups

In terms of PAG problems, more than half (57.0%) of adolescents presented with gynecologic inflammation symptoms at the first clinical visit (Table 2). Diagnoses related to early puberty and consultation of growth and development accounted for 18.2% and 10.2% of first visits, respectively. The proportion of other conditions such as gynecological examination, menstrual disorder, other endocrine problems, genital trauma, masturbation syndrome, anomalies of the genital tract, and genital tumor ranged from 0.5% to 5.6%. The patterns of PAG problems were different across different age groups. Among pediatric patients under 6 years of age, genital inflammation was the most common presentation (78.5%), followed by early puberty, and gynecological examination, accounting for 11.4% and 5.2% of the cases, respectively. Among patients aged 7 to 9 years, the top three diagnoses were genital inflammation (43.4%), early puberty (39.6%), and consultation of growth and development (10.4%). As for the patients aged 10 to 18 years, 34.9% of their first PAG clinic visits were for consultation of growth and development; the remaining cases were genital inflammation (21.4%), menstrual disorder (20.7%), gynecological examination (9.4%), early puberty (7.2%) and other endocrine problems (4.1%). The distribution of PAG problems across different age groups with an interval of two years is shown in Figure S1. The age range for which genital inflammation represented the highest proportion of cases was 0-8 years, while the percentage of the disease dropped below 50% for patients aged 8 and above. Other diseases with significant age peaks included early puberty (ages 6-10), consultation of growth and development (ages 10-14), and menstrual disorder (ages 12-18).

PAG patterns by year and season

In terms of PAG patterns over time, genital inflammation was the most common reason for PAG visits consistently over the 13-year period (Figure S2). The proportion of patients with genital inflammation increased from 48.1% in 2006 to 68.0% in 2018. Furthermore, the proportion of patients that presented with early puberty and gynecological examination fluctuated over time with a decreasing trend after 2009. The percentage of patients visiting for a consultation on growth and development increased over time and remained around 10% after 2010. The percentage of menstrual disorder cases also increased over time, while the proportion of the other diseases was relatively stable. Summer was the peak season for clinical visits for most PAG problems (Figure 2). The number of genital inflammation cases was consistently higher than other PAG problems across the four seasons (Figure S3).

Systematic review

The summarized result for all studies in China were shown in Figure 3A. In general, the top two diseases based on the weighted average ratio were genital inflammation and menstrual disorder across 33 studies. The random pooled ES was 33.7% (95% CI 22.7% to 45.5%) for genital inflammation, and 23.0% (95% CI 15.9% to 31.0%) for menstrual disorders (Figure S4A and S4B). Overall heterogeneity was significant among studies evaluating genital inflammation and menstrual disorder with I^2 (test for heterogeneity) being 99.80% and 99.62% respectively, indicating substantial heterogeneity in different studies. In the stratified analyses by clinic setting, we observed a different pattern of PAG issues between outpatients and inpatients studies. For inpatient studies, the most frequent diseases were genital tumor, menstrual disorder and genital

inflammation (Figure 3B). For outpatient studies, genital inflammation is the mainly observed among all gynecological diseases (48.8%), followed by menstrual disorders (25.2%), other endocrine problems (7.2%), early puberty (5.6%) and genital trauma (4.7%). The proportion of other diseases were less than 4% (Figure 3C).

Discussion

In this retrospective study of 97,252 patients visited at a PAG clinic in a children's hospital in eastern China over 23 years, we observed that genital inflammation was the most common presentation followed by early puberty, consultation of growth and development, gynecological examination, and menstrual disorder. The number of PAG patients and the percentage of genital inflammation increased substantially over the 13-year period. Furthermore, the disease pattern varied across age groups, with the most common gynecological issues for each age group being genital inflammation and early puberty for children (ages 0-6) and teenagers (ages 7-9), and consultation of growth and development and menstrual disorder for adolescents (ages 10-18).

Our findings are consistent with the very few long-term studies conducted outside of China, which describe the overall pattern and characteristics of PAG problems. For example, in a study conducted in a district hospital in the U.K.,⁷ recurrent vulvovaginitis and labial adhesions, which were both categorized as genital inflammation in our study, were the two most frequent reasons for demanding professional PAG treatment among 800 patients over 15 years. The UK study also showed that aside from genital inflammation, early puberty was the most common problem in patients aged 7-9, and dysmenorrhea and/or menorrhagia were the most frequent issues for patients at the age of 14. Moreover, it was also mentioned that genital inflammation and menstrual complains were kind of the leading reasons for a medical care and the most common complains of all patients.⁸

Another study conducted in the U.K. based on a tertiary hospital observed that patients of suspected genital tract anomalies and disorders of sex development accounted for more than half of the 985 patients over 16 years. Other diseases like vulvovaginal conditions, pelvic pain and cysts, labial dysmorphism, menstrual disorders, and precocious puberty formed 6% - 8% of referrals.⁹ A relatively different disease spectrum was observed in this study. In Mugdha's study anomalies of the genital tract was the most common problems among the study patients, while this gynecological condition took a relatively small proportion in our study. One potential reason may be that patients with anomalies of the genital tract tended to seek medical care at the tertiary clinic. Meanwhile, genital inflammation, which was encountered frequently in our study, only accounted for less than 15% in Mugdha's study. The difference may be explained by the fact patients with more serious diseases such as the anomalies of the genital tract tended to be referred to the tertiary hospitals for further treatment.

Regarding the PAG disease pattern in the Chinese population, our systematic review included thirty-three studies conducted between January 2005 and December 2018 among 26 cities from 14 provinces. The studies were all published in Chinese journals. Due to differences in age coverage, sampling area, sample size, clinical setting (20 outpatient and 13 inpatient settings) and other reasons, the proportion of different PAG issues were highly heterogeneous across studies. After standardized classification, the weighted percentage of the disease spectrum was found to be similar to the findings in the current study. In particular, genital inflammation and menstrual disorder were the top two PAG issues in the meta-analysis. It is worth noting that genital tumor and genital trauma ranked high in the meta-analysis, driven by 13 studies at inpatient settings which had very high proportions of these patients. One reason could be that the conditions of inpatients is generally more severe than that of outpatients. Consequently, the proportion of genital tumor and genital trauma in inpatient-based studies was relatively higher, which raised the proportion of genital tumor and genital trauma in meta-analysis. What's more, in the process of meta-analysis, we found that the classification standards of outpatient diseases in many PAG fields were widely different in China, which may affect the accuracy of the research to a certain extent.

The most common PAG disease in this study was clinically nonspecific gynecologic inflammation. This disease is closely related to improper urination habits,¹⁰ personal hygiene,^{11,12} and other factors including education,

economic status,¹³ nutrient deficiency (such as vitamin A and β -carotene),¹⁴ and higher consumption of energy-dense, high-glycemic index foods and parental awareness of the reproductive health.^{11,15} The number of patients with genital inflammation was particularly high during the summer, which might be because the high temperature in summer increased the local temperature and humidity of the female perineum, thus making bacteria or candidiasis more prone to replication and causing infection.¹⁶ The other reason of the more frequent medical visits in summer may be that parents and children had more time during the summer holiday to seek gynecological examination and consultation at the PAG clinic. For genital inflammation among children and adolescents, first-line management usually includes a review of hygiene behavior and appropriate behavioral advice unless there are concocters of other underlying pathology or sexual abuse.¹⁷ Moreover, effective health promotion programs are needed to prevent or reduce the occurrence of genital inflammation.

Early puberty was mainly concentrated at ages 7-9, while the average age of menstruation among Chinese girl was 13 years old.¹⁸ The physical condition of 7-9 age may be influenced by a variety of factors, including emotional fluctuations, stress from entering school and taking examinations, environmental changes and malnutrition. Ovarian function can be very unstable at this stage, which may lead to early puberty. Consultation of growth and development and menstrual disorders were the main complaints of the 10-18 age group. After the age of 10, girls begin to experience menarche, which is often thought of as a sign of starting to maturity.¹⁹ If teenagers are growing and developing behind or overstepping their peers at this time, many parents may feel anxious and take them to the hospital for help. However, as the regulatory functions of the hypothalamus and pituitary are not fully mature, stable periodic regulation with the ovary has not yet been established.^{19,20} During this process, physiological and psychological disorders might lead to the occurrence of various menstrual diseases such as dysfunctional uterine bleeding, dysmenorrhea and amenorrhea.²¹ Other PAG issues including genital trauma, masturbation syndrome, anomalies of the genital tract, and genital tumor were less common in our study population. However, these diseases were relatively severe. They were sent to inpatient ward for further treatment which imposed a heavy burden on individuals and families, suggesting the need for more attention and support.²

Utilizing clinical medical record data collected over one decade based on the first PAG clinic visit, this study represents the first large-scale study with the longest time-span describing the spectrum of gynecological issues in both pediatric and adolescent patients in China. The large sample size, long time span and wide range of conditions provides a better understanding of PAG problems, a highly neglected issue in China and worldwide. However, there were several limitations to this study. Firstly, the patient's diagnosis at first clinical visit may not be the final diagnosis. There may have been additional tests conducted after the initial visit, which may have altered the diagnosis. Nevertheless, the diagnosis at first clinical visit was easy to use for describing the overall patterns of PAG issues in this large study base. Secondly, the results of this study are based on medical records from a single center, which may not represent the PAG disease spectrum in other regions of China.

Children and adolescents with PAG issues have received increasing attention from the global community. For example, an International Fellowship of Pediatric and Adolescent Gynecology (IFEPAG), an international diploma of recognition, has been founded facilitated by the International Federation of Pediatric and Adolescent gynecology (FIGIJ).¹ North American Society for Pediatric and Adolescent Gynecology (NASPAG) have designed short and long curriculums and develop them continuously to provide professional knowledge for the postgraduate trainees in obstetrics and gynecology in residency programs.²² However, there remains a major shortage of PAG clinics all over the world, especially in underdeveloped countries and regions.²³⁻²⁴ The high costs, insurance issues, stigma, absence of PAG education to community health service providers led to the residents' difficulties in access to specialists and the lack of place for better care by someone closer to the family's home. These barriers put a huge workload on doctors and increased the cost of medical care for patients, which also led to lengthy diagnostic delays. Therefore, it is imperative to establish a PAG service network to provide standardized clinical, educational and referral pathways and to secure the gynecological and reproductive health of children and adolescents in China.

Our study aimed to establish a spectrum of PAG diseases to advocate for and alongside young females to achieve specialized and expertized gynecological care and support. In China, embarrassment, privacy concerns, or other cultural factors are usually barriers to women visiting gynecologists, and this may be exacerbated among children and adolescent girls. Professional gynecology research and guidance can play an important role in popularizing gynecology education, removing public stigma, and reducing health and social inequality in this field. Therefore, our findings could help health care providers and investigators gain insight into the specific medical needs of this particular population group, which could inform future targeted clinical investigations and healthcare quality improvement programs.

Conclusion

The pattern of PAG issues at first clinical visit in China has seldom been reported in international journals. Our study helps to fill this gap by examining diagnoses at the first clinical visit over a 13-year period at a large PAG hospital in China. A major finding was that genital inflammation was the most common issue for pediatric and adolescent patients with gynecological problems. This is consistent with previous studies and the meta-analysis conducted as part of this study. The study also reveals an increased number of PAG patients in China over the decades, emphasizing the need for more healthcare services and epidemiologic research in this field.

Disclosure of interests

The authors report no conflict of interests.

Contribution to authorship

L.S. designed the study and acquired the study data. C. Y., and L. S. designed the analysis; Y. H. performed the statistical analyses; Y. J., interpreted the data; Y. J. drafted the manuscript; Y. J., C. Y., J.M. and H. G. revised the manuscript; C. Y. and J.M. supervised the data analysis and interpretation; L.S. and C.Y. had the primary responsibility for the study final content. All authors critically reviewed the manuscript and approved the final draft.

Details of ethics approval

The study was approved by the Human Subjects Committees of the Children's Hospital, Zhejiang University School of Medicine. The ethical approval number was 2019-IBR-103. Date of approval 22nd August 2018.

Details of patient's consent

This study was a secondary analysis project based on the existing medical record de-identified data, which was exempted from human subject informed consent.

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