INPLASY PROTOCOL

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None declared.

GnRHa increases the morbidity of PCOS in children with CPP

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Review question / Objective: **We conducted this systematic review and meta-analysis to evaluate the morbidity of PCOS of GnRHa treatment in children with CPP in order to provide the reference of the long-term safety of GnRHa therapy.**
Patient, Participant, or population: **In the spectrum of CCP, patients presented thelarche, pubarche (TANNER score of at least 2 prior to the age of 8 years), or bone age advancement, and a serum LH concentration of 5 U/L after GnRH (or leuprolide) administration or a basal LH level of 0.3 U/L using ultra-sensitive assays.In the spectrum of PCOS, patients met the 2003 Rotterdam criteria.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 January 2023 and was last updated on 04 January 2023 (registration number INPLASY202310010).

INTRODUCTION

Review question / Objective: **We conducted this systematic review and meta-analysis to evaluate the morbidity of PCOS of GnRHa treatment in children with CPP in order to provide the reference of the long-term safety of GnRHa therapy.**

Condition being studied: **Central precocious puberty (CPP) results from premature activation of the hypothalamic–pituitary–gonadal axis (HPGA) and is commonly characterized by the early development of pubertal biochemical and physical features before 8 years of age for girls and 9 years of age for boys. The overall prevalence of CCP was approximately 1 /5000–10,000 children, with a 5- to 10-fold higher incidence in girls than in boys, in which idiopathic CPP (ICPP) is the most frequent form, accounting for approximately 90% cases of CPP in girls. CPP is associated with a lower final adult height (FAH), potential sexual abuse, increased risk of psychological**

disturbances and increased risk of developing cardiovascular diseases and reproductive tract cancers. Gonadotrophin-releasing hormone analog (GnRHa) is a synthetic peptide drug that is modelled based on human hypothalamic gonadotropin-releasing hormone (GnRH), which is designed to act on the anterior pituitary. GnRHa interacts with the GnRH receptor and stimulates the synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the initial phase of administration. Sustained release of GnRHa suppresses the production of FSH and LH, which in turn suppress the production of sex hormones by the gonads. Several pharmaceutical formulations of GnRHa, such as buserelin, histrelin, leuprorelin, triptorelin and goserelin, are available and used clinically. The choice of drug and duration of treatment depend on the unique growth and development needs. GnRHa has been a treatment choice for CPP since the mid-1980s, and its effects on HPGA suppression has been generally recognized.

However, the long-term safety of GnRHa treatment in gynaecology field remains unclear, and some studies have reported contradictory findings. Before 2000, Boepple observed PCOS in approximately half of the patients treated with GnRHa, whereas Bridges et al. reported a prevalence of 24% of PCOS during GnRHa therapy compared with only 2% in an age-matched control group. However, the criteria used for PCOS diagnosis were not uniform in the two studies. Furthermore, in a before-after study, Franceschi et al. reported 30% prevalence of PCOS in young women with ICPP treated with GnRHa, according to the Rotterdam criteria. The occurrence of PCOS in CCP patients receiving GnRHa were still heterogeneous in the recent 12-year literatures.

METHODS

Search strategy: A systematic study was conducted by two reviewers, searching literature in databases including CNKI, Wanfang, VIP, PubMed, Embase, and the Cochrane Library. The keywords in text and MeSH terms were as follows: GnRHa (synonym including "GnRH-a" and "Gonadotrophin releasing hormone agonist"), PCOS (synonym including "polycystic ovary syndrome") and CPP (synonym including " sexual precocity," “pubertas praecox,” and “central precocious puberty”). The date for inclusion was from January 1, 2010 until October 1, 2022. The data were screened, selected, extracted and cross-verified by two reviewers independently.

Participant or population: In the spectrum of CCP, patients presented thelarche, pubarche (TANNER score of at least 2 prior to the age of 8 years), or bone age advancement, and a serum LH concentration of 5 U/L after GnRH (or leuprolide) administration or a basal LH level of 0.3 U/L using ultra-sensitive assays.In the spectrum of PCOS, patients met the 2003 Rotterdam criteria.

Intervention: The experimental group was administered GnRHa with no limitation on the drug name, intake frequency per day and course in the included cohort studies. All the patients in experimental groups received GnRHa per 28 day with the maximum dosage of 3.75mg.

Comparator: The control group was treated with non-GnRHa or received none treatment.

Study designs to be included: Cohort studies published in Chinese and English, in which GnRHa was applied in the treatment of CPP.

Eligibility criteria: (1) duplicate publications; (2)no target outcomes; (3) missed data and incapability of contacting the investigator; (4)treatment combined with growth hormone.

Information sources: CNKI, Wanfang, VIP, PubMed, Embase, and the Cochrane Library.

Main outcome(s): The morbidity of PCOS.

Data management: Microsoft Excel was used for data extraction. The data collected

from each included study and cross-checked by two researchers were as follows: (1) Year of publication; (2)Name of first author; (3) Region; (4) Patient features; (5) Sample size; (6) Intervention; (7) PCOS outcome. Any different conclusions between the 2 searchers were discussed with a third researcher for settlement.

Quality assessment / Risk of bias analysis: The quality of observational cohort studies was evaluated using the Newcastle-Ottawa Scale was applied to evaluate the risk of bias of the included cohort studies. 3 aspects were included (maximum 9 points): (1)selection (representativeness of cases, selection of controls, ascertainment of exposure, and demonstration that the outcome of interest was not existent at the beginning of the study); (2)comparability (comparability of cohorts based on the design or analysis); (3) outcome (evaluation of outcome, length of follow-up necessary for outcomes to occur, appropriateness of follow-up of cohorts). Quality was scored as: low (0–3), moderate (4–6), and high (7–9 points). Any different conclusions between the 2 searchers were discussed with a third researcher for settlement.

Strategy of data synthesis: RevMan 5.1 software was used for Meta-analysis. Dichotomous variables were presented with the response ratio (OR). Heterogeneity was detected through the $\chi 2$ test. $p > 0.1$ and $I2 < 50\%$ indicated a low heterogeneity among cohort studies, thus the fixed effect model (FEM) was preferred. $p < 0.1$ and $I2 \geq 50\%$ indicated a significant heterogeneity, thus the random effect model (REM) was preferred.

Subgroup analysis: Subgroup analysis was conducted based on the follow-up time and treatment course to search the underlying reasons of heterogeneity.

Sensitivity analysis: The stability of statistic outcomes was evaluated through sensitivity analysis and a funnel plot was used to assess publication bias.

Language restriction: English, Chinese.

Country(ies) involved: China.

Keywords: GnRHa, PCOS, CCP, meta-analysis.

Contributions of each author:

Author 1 - Yue Shi designed the study, collected, analyzed the data and drafted the manuscript.
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