Journal of Pediatric Surgery 49 (2014) 1659–1667

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Review Article

Hormonal therapy using gonadotropin releasing hormone for improvement of fertility index among children with cryptorchidism: a meta-analysis and systematic review ☆

Michael E. Chua [a,*], Jonathan S. Mendoza [b], Michael John V. Gaston [c], Saturnino L. Luna Jr. [a], Marcelino L. Morales Jr. [d]

[a] Institute of Urology, St. Luke's Medical Center, Quezon City, Philippines
[b] Department of Preventive and Community Medicine, St. Luke's College of Medicine, Institute of Urology, St. Luke's Medical Center, Quezon City, Philippines
[c] Department of Surgery, Ateneo Medical School, Philippine General Hospital, Manila, Philippines
[d] Institute of Urology, St. Luke's Medical Center, Department of Urology, National Transplant and Kidney Institute, Quezon City, Philippines

ARTICLE INFO

Article history:
Received 15 February 2014
Received in revised form 28 May 2014
Accepted 22 June 2014

Key words:
Cryptorchidism
Gonadotropin releasing hormone
Fertility index
Sperm parameters
Meta-analysis
Systematic review

ABSTRACT

Background/Purpose: Gonadotropin releasing hormone(GnRH) as an adjunct to orchidopexy for the treatment of cryptorchidism is still controversial. Present evidences were studied through a meta-analysis of comparative clinical trials.
Method: Systematic literature search was done up to September 30, 2013. Studies were independently appraised by two reviewers. Continuous data of fertility indices were extracted as weighted mean difference (WMD) and standard deviation (SD); while nominal data of fertility indices were extracted as relative risk (RR). Random effects model was used to analyze the pooled effect estimates. Inter-study heterogeneity and publication bias were assessed. PROSPERO Protocol registration (CRD42013004922).
Results: Ten eligible studies were included. The pooled effect estimates showed that cryptorchid children treated with GnRH when compared with controls, have significantly increased germ cell per tubule (WMD: 0.35; 95% CI 0.07–0.62, $P = 0.01$) and increased RR to have normal value of germ cell per tubule (RR: 2.86; 95% CI 1.73–4.71, $P < 0.0001$). Inter-study heterogeneity was noted, source identified with subgroup analysis. Publication bias was not evident. No GnRH related adverse events were reported in all studies.
Conclusion: Evidence suggests that a subset of boys with cryptorchidism may benefit from GnRH as adjunctive to orchidopexy in improving the fertility index. However, future studies are recommended to specifically identify subgroup characteristics of cryptorchidism that will clearly benefit from the treatment.

1. Background

Cryptorchidism is one of the most common urogenital anomalies noted among neonates, with a 30% incidence among pre-term neonates and 3% among full term babies [1]. Several studies have illustrated the importance of early surgical intervention (<1 year old) to preserve the future fertility potential. However, even with early orchidopexy, it was noted that approximately 32% of patients with bilateral and 10% with unilateral cryptorchidism will develop azoospermia in adulthood; which may somehow affect paternity rates [2].

Hormonal therapy used to induce testicular descent have low success rates (≤20%) and high reascent rates (15%), hence, was not recommended as standard of treatment [3]. However, in the latest guidelines by the European Society for Pediatric Urology published in 2013, it was stated that the medical treatment with orchidopexy may be beneficial in terms of increasing the fertility index [4]. The suggestion was based on the theoretical rationale that the predictor of male fertility is dependent on the germ cell condition during the post-natal age, particularly at the "mini-puberty" at 3–9 months postnatal period; which is by large an androgen dependent process [5]. The adjunctive hormonal therapy to surgery, particularly the Gonadotropin Releasing Hormone (GnRH) is assumed to increase testicular germ cell maturity by simulating the neonatal gonadotropin surge thereby elevating the testicular testosterone level; which is believed to improve future fertility [5].

In recent years, use of hormonal adjunctive therapy stirred controversies when several studies showed no improvement with the use of HCG on testicular conditions. Adding that it aggravated the deteriorating testicular growth by inducing germ cell apoptosis [6–8]. However, some experts in the field would want to reconsider the hormonal therapy with GnRH, since most of the studies that showed adverse effect were all using HCG and none of GnRH [4,9]. Hence, with the paucity of consensus and

☆ Disclosure: No financial support was received for the execution of this research project. All full text articles were requested from the libraries of Harvard University–Boston Children's Hospital, University of Toronto–Hospital for Sick Children and St. Luke's College of Medicine.
* Corresponding author at: Institute of Urology, St. Luke's Medical Center, 279 E. Rodriguez Sr. Blvd., Cathedral Heights, Quezon City, Philippines. Tel.: +63 922 8372 180.
E-mail address: auhc_ekim@yahoo.com (M.E. Chua).

http://dx.doi.org/10.1016/j.jpedsurg.2014.06.013
0022-3468/

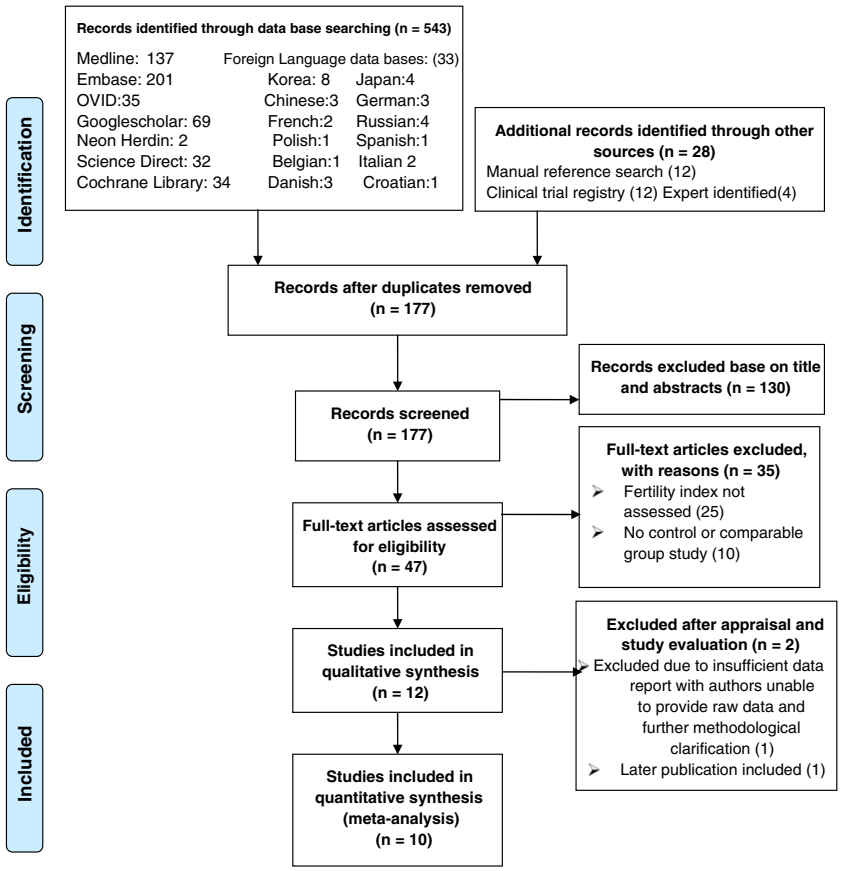

Fig. 1. PRISMA flow diagram of literature search and selection for meta-analysis and systematic review.

inconsistent evidences, the objective of the study is to present and summarize the latest available evidences on the effect of hormone therapy using GnRH on fertility indexes among boys with cryptorchidism through a meta-analysis of comparative clinical trials.

1.1. Methodology and protocol

The protocol of this review was registered in PROSPERO registry for systematic reviews (CRD42013004922) and was made in consultation with methodological and content experts and is compliant to the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

The systematic literature acquisition was conducted by two independent physician reviewers using the same search strategy with Medical subject heading (MeSH) and common search terms: ("Cryptorchidism" [MeSH] OR "undescended testis") AND ("Hormonal therapy" OR "Luteinizing Hormone-Releasing Hormone" OR "Chorionic Gonadotropin" [MeSH] OR "Gonadotropin-Releasing Hormone" [MeSH with no limit or filter used. Non-English articles were also considered from the following electronic biomedical databases: MEDLINE, EMBASE, OVID, Google scholar, Neon Herdin, Cochrane Library databases and other foreign language biomedical databases (http://www.e-meducation.org/medical_resources/biomedical-databases). Unpublished and ongoing clinical trials that are relevant to the subject was searched from the clinicaltrial.gov and WHO.int trial registries. Likewise, expert consult and peer review identified literatures were also included for consideration. The initial literature search was done on June 30, 2013 and updated search was on September 30, 2013.

This systematic review considered only comparative studies, such as randomized-controlled trials, cohorts and case-control studies that were able to study the effect of pre- or post orchidopexy GnRH hormonal treatment with or without HCG for at least four weeks duration and had a comparative group of subjects who underwent orchidopexy. These clinical trials included only infants and children with undescended testis (unilateral/bilateral) with parental consent for hormonal therapy, orchidopexy, and testicular biopsy [for case-control studies and RCTs]; or adolescent and adult participants with history of cryptorchidism, who had previous adjunctive/neoadjunctive GnRH therapy to orchidopexy in childhood and consented for semen analysis [for cohorts]. Likewise all studies excluded patients with retractile testis, previous groin surgeries, ectopia or abdominal testicular location, secondary cryptorchidism, hormonal disorders, previous hormonal treatment, testicular anomalies/pathologies, and inconclusive testicular biopsy results. Primary outcome considered for this review is the fertility index, such as the paternity rate, semen analysis on longitudinal follow-up and number of mature germ cells per tubule as measured on testicular biopsy in children. Adverse events reported from each study were also identified and summarized in this review.

Two independent physician reviewers did an independent literature selection, evaluation and appraisal using the Critical Appraisal Skill Programme from National Health Service (CASP-NHS) [11]. Only trials with appraisal scores of at least 8 out of 11 were considered for further inclusion and evaluation. Identified primary outcome data from each included study were summarized and extracted using a standardized form adapted from Cochrane Collaborative Review Revman 5 [12]. Bias and random error in analysis among the RCTs were evaluated using the Cochrane methods of assessing risk of bias [13]. While methodological quality of case-controls and cohorts were assessed using Newcastle-Ottawa quality assessment scoring. All eligible studies were fully reviewed to assess and minimize reporting bias, publication bias, within trial reporting bias and their potential impact on overall effect measure. For accurate