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Meta-Analysis

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Gonadotropin-Releasing Hormone Analogue Stimulation Test Versus Venous Sampling in Postmenopausal Hyperandrogenism

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Abbreviations: APG, adrenal:peripheral gradient; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; FN, false negative; FP, false positive; GAST, GnRH analogue stimulation test; GnRH, gonadotropin-releasing hormone; GnRHa, GnRH analogue; HSROC, hierarchical summary receiver operator characteristics curve; OH, ovarian hyperthecosis; OPG, ovarian:peripheral gradient; PET/CT, positron emission tomography/computed tomography; PH, postmenopausal hyperandrogenism; ROC, receiver operator characteristic; SOAVC, selective ovarian and adrenal vein catheterization; TN, true negative; TP, true positive; VT, virilizing tumor.

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Abstract

Postmenopausal hyperandrogenism can be due to excessive androgen secretion from adrenal or ovarian virilizing tumors or nonneoplastic conditions. The etiology of postmenopausal hyperandrogenism can be difficult to discern because of limited accuracy of current diagnostic tests. This systematic review compares the diagnostic accuracy of the gonadotropin-releasing hormone (GnRH) analogue stimulation test against selective ovarian and adrenal vein sampling of androgens in distinguishing neoplastic from nonneoplastic causes of postmenopausal hyperandrogenism. Diagnostic test accuracy studies on these index tests in postmenopausal women were selected based on preestablished criteria. The true positive, false positive, false negative, and true negative values were extracted and meta-analysis was conducted using the hierarchical summary receiver operator characteristics curve method. The summary sensitivity of the GnRH analogue stimulation test is 10% (95% confidence interval [CI], 1.1%-46.7%) and that for selective venous sampling is 100% (95% CI, 0%-100%). Both tests have 100% specificity. There is limited evidence for the use of either test in identifying virilizing tumors in postmenopausal hyperandrogenism.

Key Words: Postmenopausal hyperandrogenism, gonadotropin-releasing hormone analogue stimulation test, selective adrenal and ovarian vein catheterization, virilizing tumors, ovarian neoplasms, adrenal neoplasms

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Postmenopausal hyperandrogenism (PH) is a state of androgen excess originating from the adrenal glands or the ovaries, manifesting with increased terminal hair growth or virilization [1]. Current diagnostic tests may not be able to distinguish PH due to virilizing tumors (VT) from other forms of functional hyperandrogenism. Basal testosterone levels above 100 to 140 ng/dL in conjunction with abrupt onset and rapid progression of hyperandrogenic features may indicate the presence of VT [1]. However, basal androgen levels overlap between various etiologies of PH [2-4] and diagnostic cutoff values vary widely [5-8]. Furthermore, VT may not secrete substantial amounts of androgens [2, 9, 10]. Small VT may evade detection on scans [11-13]. Scans are also not helpful in distinguishing adrenal VT from incidentalomas [14-16] and ovarian VT can coexist with ovarian hyperthecosis (OH) [13]. Positron emission tomography/computed tomography (PET/CT) is not well-studied in PH [1, 11]. The gonadotropin-releasing hormone (GnRH) analogue stimulation test (GAST) has been used to evaluate women with hyperandrogenism. Following a single intramuscular injection of long-acting or short-acting GnRH analogue (GnRHa), ovarian production of androgen should be suppressed [17]. With short-acting GnRHa, testosterone should fall by at least 50% from baseline value while with long-acting GnRHa, testosterone levels fall into the reference interval [3]. GAST is noninvasive, does not require technical expertise, and can be conducted in the outpatient setting. However, it is performed over 3 months so the diagnosis of VT can be delayed. Selective ovarian and adrenal vein catheterization (SOAVC) localizes VT based on differential gradients in androgen levels between ovarian, adrenal, and peripheral veins. SOAVC requires expertise and success rates in cannulating all veins are from 26% to 66% [18-20]. It is invasive, exposes patients to radiation, and carries the risk for contrast nephropathy. Furthermore, SOAVC is unreliable when ovarian VT and OH coexist.

Rational for Conducting This Systematic Review

The investigations for PH have limited diagnostic accuracy and can be invasive. As GAST is a simple and noninvasive test, we compared its diagnostic accuracy against SOAVC in distinguishing neoplastic from nonneoplastic causes of PH. This is the first systematic review on this topic.

Objectives

The aim of this systematic review is to compare the diagnostic accuracy of GAST and SOAVC in distinguishing neoplastic from nonneoplastic causes of PH. The reference standard is the combination of clinical evaluation, biochemical evaluation, abdominal and pelvic imaging, and histological confirmation of tumor. The aim was achieved by:

1. Performing a systematic review of all diagnostic test accuracy studies evaluating the use of GAST and SOAVC in PH
2. Performing meta-analysis if the results are sufficiently homogeneous and providing a narrative summary of the results if otherwise

Methods

Eligibility Criteria

Diagnostic test accuracy studies in which information on index tests and reference standards are available were included for analysis. Only studies that included postmenopausal women were included. There was no restriction on the language, publication status, or date of publication of studies.

Participants

Studies which reported the accuracy of GAST, SOAVC, and reference standards in identifying sources of androgen secretion in PH were included.

Index Tests

GAST using short-acting or long-acting GnRHa and SOAVC.

Reference Standard

The identification of sources of androgen secretion in PH based on clinical features, basal androgen levels, imaging tests such as computed tomography (CT), magnetic resonance imaging, and/or ultrasound of the adrenal glands and ovaries, laparoscopic findings (where available), follow-up data, and histology is regarded as the reference standard.

Target Condition Being Diagnosed

Postmenopausal hyperandrogenism.

Exclusion Criteria

Studies unrelated to PH, GAST, or SOAVC were excluded. Studies that did not include postmenopausal women were excluded.

Outcomes

True positive (TP), false positive (FP), false negative (FN), and true negative (TN) values of each test were extracted.

Assessment of Methodological Quality

Quality of evidence of studies was assessed by 2 reviewers (E.L.T. and J.M.M.T.) using the QUADAS-2 tool. The reasons for classifying risk of bias as low, unclear, or high for each domain were recorded.

Statistical Analysis and Data Synthesis

Characteristics of included and excluded studies were summarized. Meta-analysis was conducted on studies that reported TP, FP, FN, and TN values. The hierarchical summary receiver operator characteristics curve (HSROC) method was used in meta-analysis as this model allows combination of different cutoff values of GAST and SOAVC in the studies. It also allows comparison of ROCs of different androgen assays in the studies. Statistical analysis was performed using the online app MetaDTA: Diagnostic Test Accuracy Meta-Analysis v1.25 [21]. Flow diagrams, risk of bias charts, forest plots, and ROCs were generated using the Review Manager 5.3 software [22]. Summary of findings tables were generated using the GRADEpro GDT online app [23].

Assessment of Reporting Bias

Reporting bias was assessed by comparing the number of studies that were performed against the number of studies that did not report the accuracy measure.

The following are found in the supplementary material [24]:

1. Methods (information sources, data management, selection process, data collection process, and data items)
2. Details of included studies
3. Details of excluded studies
4. Risk of bias and applicability concerns assessment
5. Summary of findings tables
6. Assessment of reporting bias

Search Strategy

The search strategies for this systematic review can be found on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/).

Results

Results of the Search

A total of 13 597 records were retrieved from MEDLINE (2374), Embase (8387), CINAHL (415), DARE (34), Cochrane Library (339), SCI Expanded (1595), PROSPERO (19), ClinicalTrials.gov (60), and WHO ICTRP (374). A further 34 articles were found through manual searching of reference lists of shortlisted articles. The study flow diagram is shown in Fig. 1. Duplicates (3088) were excluded, and 10 473 irrelevant studies were excluded after screening the titles and abstracts. Seventy articles were retrieved for full-text screening. Of these, 64 were excluded (see "*F. Characteristics of excluded studies*"). Ultimately 6 studies fulfilled the inclusion criteria: 3 studies on GAST and 3 studies on SOAVC. These 6 studies had sufficiently homogeneous data for meta-analysis.

Characteristics of Included Studies

The characteristics of included studies are summarized in Table 1.

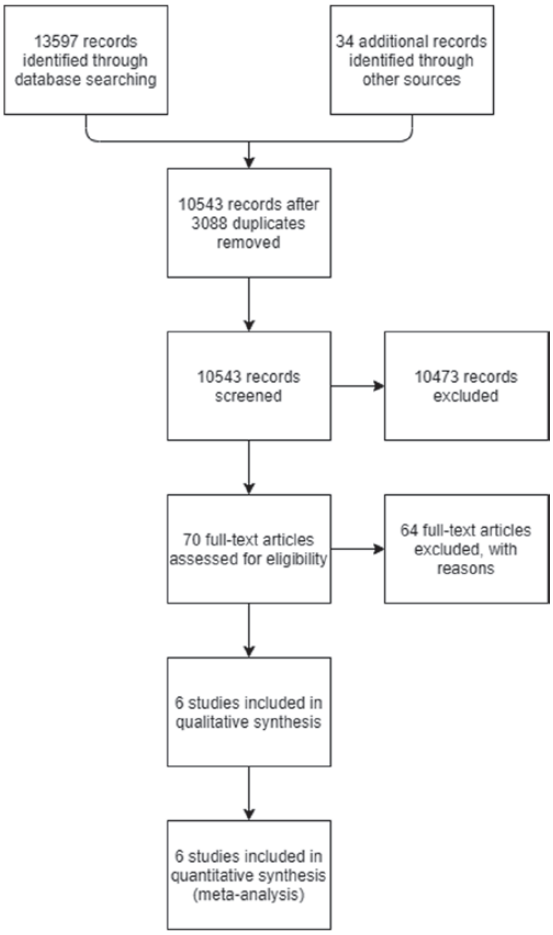

Figure 1. Study flow diagram.

Table 1. Characteristics of Included Studies

Study	Study characteristics and setting	Index test	Target condition and reference standard(s)
Bricaire 1991 [26]	16 patients with plasma testosterone levels exceeding 1.4 ng/mL and whom US and CT failed to locate VT. 6 were found to have VT (2 lipid cell tumors, 2 Leydig cell turmours, 1 serous papillary cystadenoma with functioning stroma, 1 adrenocortical carcinoma), 6 had polycystic ovaries, 4 had stromal/hilar cell hyperplasia. Teaching hospital in France.	Bilateral ovarian-adrenal vein catheterization. Testosterone, androstenedione, cortisol, urine free cortisol, and 17-hydroxyprogesterone were measured using RIA.	Hyperandrogenism due to VT. Clinical evaluation, biochemical evaluation, abdominal and pelvic imaging, and histological confirmation of VT.
Gomes 2016 [25]	18 hyperandrogenic women with normal adrenal CT. 5 had VT (3 Leydig cell turmours, 1 steroid cell tumor, 1 teratoma), 13 had OH. University hospital in Brazil.	Leuprolide acetate 3.75mg was given every 30 days for 3 months. Positive test is defined as failure of testosterone to fall by more than 50% from baseline value. Testosterone levels were measured before and 30 days after the last leuprolide injection. The types of assays used were not stated.	Hyperandrogenemia of ovarian origin. Histological confirmation of VT.
Kaltsas 2003 [18]	42 women who underwent SOAVC. 8 had VT (2 adrenal adenomas, 1 Leydig cell tumor, 2 Sertoli-Leydig cell tumors, 1 hilus cell tumor, 1 granulosa cell tumor; histology not available for 1 patient). 30 had nontumoral hyperandrogenism. Results were not available in 4 patients. Tertiary hospital in the United Kingdom.	Transfemoral selective catheterization of ovarian and adrenal veins. Estradiol OPG >2 confirms cannulation of ovarian vein. Cortisol APG >2 confirms cannulation of adrenal vein. Testosterone OPG or APG >2 localizes androgen source to the specific vein. Testosterone, androstenedione, and DHEAS were measured using standard immunoassays in the Chemical Endocrinology Department of Saint Bartholomew's Hospital, United Kingdom.	Hyperandrogenism due to VT. Clinical evaluation, biochemical evaluation, adrenal CT, pelvic ultrasound, and histological confirmation of VT.
Pascale 1994 [17]	5 women referred for clinical symptoms of virilization with testosterone levels greater than 7 nmol/L and normal DHEAS. 3 had VT (1 granulosa cell tumor, 1 hilus cell tumor, 1 Sertoli-Leydig cell tumor). 2 had OH. France.	Single intramuscular injection of 3.75mg of D-Trp-6-GnRH was given. Positive test was defined as failure of testosterone to fall into the range seen in controls. Testosterone, androstenedione, DHEA, DHEAS, FSH, and LH were measured by RIA before and 3 weeks after GnRHa administration.	Hyperandrogenism due to ovarian VT.

Table 1. Continued

Study	Study characteristics and setting	Index test	Target condition and reference standard(s)
Sörensen 1986 [27]	75 women who underwent SOAVC between 1976 and 1986. 67 women had hyperandrogenism and 8 women were healthy volunteers with ovulatory cycles. 7 had VT (3 lipid cell tumors, 2 Leydig cell tumors, 2 Sertoli-Leydig cell tumors). 60 had nontumoral hyperandrogenism. Department of Radiology, Klinikum Steglitz, Free University of Berlin, Germany.	Transfemoral selective catheterization of ovarian and adrenal veins. Testosterone OPG >2.7 ng/mL localizes androgen source to the specific ovarian vein. DHEAS, 17-hydroxyprogesterone, and cortisol were measured by direct RIA Testosterone, dihydrotestosterone, androstenedione, and DHEA were measured by RIA after celite chromatography.	Hyperandrogenism due to VT. Clinical evaluation, biochemical evaluation, abdominal and pelvic imaging, endoscopy, and histological confirmation of VT.
Yance 2017 [13]	34 postmenopausal women with ovarian VT and OH were studied retrospectively. 13 had VT (5 Leydig cell tumors, 4 steroid cell tumors, 1 thecoma, 3 Sertoli-Leydig cell tumors). 21 had OH. Tertiary center in Brazil.	3.75mg of leuprolide acetate was given intramuscularly every 30 days for 3 months. Testosterone, estradiol, FSH, and LH were measured before and 30 days after the last GnRHa injection. Positive test was defined as failure of testosterone to fall by more than 50% from baseline value. Testosterone, estradiol, LH, and FSH were measured by immunofluorometric assay.	Hyperandrogenism due to ovarian VT and OH. Clinical evaluation, biochemical evaluation, adrenal CT, pelvic ultrasound, and histological confirmation of VT.

Abbreviations: APG, adrenal:peripheral gradient; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GnRHa, GnRH analogue; LH, luteinizing hormone; OH, ovarian hyperthecosis; OPG, ovarian:peripheral gradient; RIA, radioimmunoassay; VT, virilizing tumor.

Possible Sources of Heterogeneity

GAST

The conduct and cutoffs of the index tests were not standardized. Gomes et al [25] and Yance et al [13] administered 3 doses of leuprolide acetate over 3 months while Pascale et al [17] administered only a single dose of leuprolide acetate. Gomes et al and Yance et al defined a positive test as failure of testosterone to fall by more than 50% from baseline while Pascale et al defined a positive test as failure of testosterone to fall into the range seen in controls.

The reference standards were not standardized between studies. All studies established the reference standards based on clinical features, baseline androgen and gonadotropin levels, imaging tests, and histology. However, different types of scans were used. Gomes et al selected patients with normal adrenal glands based on CT scans. Pascale et al used pelvic ultrasound and adrenal CT while Yance et al used pelvic magnetic resonance imaging in 16 women, pelvic ultrasound in 32 women, and PET/CT in 5 women.

The androgen levels were reported using different units. Gomes et al and Yance et al reported testosterone levels in ng/dL. Yance et al measured testosterone using immunofluorometric assay (AutoDELFIA, WallacOy, Turku, Finland). Gomes et al did not report the type of assay for androgen measurement. Pascale et al reported testosterone in nmol/L and they used radioimmunoassay for their study.

SOAVC

The conduct and cutoffs of the index tests were not standardized. Kaltsas and colleagues [18] performed bilateral ovarian-adrenal vein catheterization in no particular order. Ovarian cannulation was confirmed using an ovarian:peripheral gradient (OPG) for estradiol above 2. Adrenal vein cannulation was confirmed using an adrenal:peripheral gradient (APG) for

cortisol above 2. Bricaire and colleagues [26] preferentially cannulated the left ovarian vein first, followed by the left adrenal vein, then right ovarian vein, and lastly the right adrenal vein, although the sequence of sampling was not rigid. Patients were given meperidine and hydroxyzine prior to insertion of the catheter. No attempts at occluding other vessels were made during blood sampling. Cannulation was confirmed using fluoroscopic guidance. OPG and APG were not prespecified. Sörensen and colleagues [27] conducted transfemoral venous catheterization by the same radiologist and the veins were sampled in random sequence. Successful cannulation was established via fluoroscopy. No premedications were given. OPG and APG were not prespecified.

The study population differed between studies. Kaltsas and colleagues studied hyperandrogenized women who failed to suppress at least one androgen by 50% following a low-dose dexamethasone suppression test. Bricaire and colleagues studied women with baseline testosterone levels above 1.4 ng/mL. Sörensen and colleagues studied 67 women with clinical or biochemical features of hyperandrogenism or hyperandrogenemia and 8 healthy premenopausal women.

The reference standards were not standardized between studies. Kaltsas and colleagues had histological confirmation in 15 of the 16 subjects in their studies. Bricaire and colleagues had histological confirmation in patients with localizing gradient on venous catheterization but not in 10 patients without lateralizing gradients. Sörensen and colleagues had histological confirmation in 18 patients but not in 60 patients whom they assumed to have no VT based on negative imaging tests.

Different imaging techniques were used in the studies. Kaltsas and colleagues obtained transabdominal ultrasound of the ovaries in most of their subjects and transvaginal ultrasound in a minority of them. CT of the adrenal glands was obtained in all subjects in their study. Bricaire and colleagues obtained ultrasound of the pelvis and CT of the adrenal glands in their patients. Sörensen and colleagues performed retrograde venography, iodocholesterol isotopic scan, and angiography in some of their patients. They also performed laparoscopy to rule out macroscopic ovarian lesions.

The androgen levels were reported using different units. Kaltsas reported the units for testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) in nmol/L. Bricaire reported testosterone in ng/mL. Sörensen and colleagues reported testosterone and DHEAS in ng/mL.

Different cutoff levels for localization were used by the authors. Kaltsas and colleagues defined localization as an OPG or APG for testosterone above 2. Sörensen and colleagues used an OPG for testosterone greater than 2.7ng/mL to localize ovarian VT. No threshold values for OPG or APG were declared by Bricaire.

Subgroup Analyses

Subgroup analysis on postmenopausal women could not be done because Gomes et al did not report the number of postmenopausal women with and without VT. Kaltsas and colleagues had 4 postmenopausal women out of 42 subjects. All postmenopausal women had VT in this study so there is no control group for comparison. Only 4 studies remain after exclusion of these 2 studies and the number of postmenopausal women in these studies is small: Pascale et al had 4 postmenopausal women out of 5 subjects (2 had VT and 2 had OH), and Yance et al had 34 postmenopausal subjects in their study. Bricaire and colleagues had 6 postmenopausal women out of 16 subjects (2 had VT and 4 had OH), and Sörensen and colleagues had 5 postmenopausal women out of 75 subjects (4 had VT and 1 had OH).

Sensitivity Analyses

Kaltsas and colleagues had low success rate in 4-vessel cannulation for SOAVC, so lateralizing OPG and APG could not be established in 5 patients in the VT group and 2 patients in the non-VT group. Sensitivity analysis was conducted for the best-case scenario (no FN, minimal FP, and maximal TN) and worst-case scenario (maximal FN, maximal FP, and minimal TN).

Characteristics of Excluded Studies

Sixty-four studies were excluded (see supplemental material). Twenty studies were excluded because they were not diagnostic test accuracy studies [6, 10, 28-45]. Twenty-two studies were excluded because they did not evaluate the diagnostic accuracy of GAST or SOAVC [5, 7, 8, 46-64]. Twenty-eight studies were excluded because they did not include postmenopausal women [39, 42, 43, 49, 58, 59, 64-85]. One study was excluded because the authors did not provide the study details despite repeated requests [86].

Findings: GAST vs SOAVC to Diagnose VT in PH

Quality of evidence was described using the GRADE framework. Prevalence of VT was derived from 2 large observational studies [87, 88].

The TP, FP, FN, and TN values reported by Gomes et al are 1, 0, 4, and 13, respectively. GAST had a sensitivity of

20% (95% confidence interval [CI] 1%-72%) and specificity of 100% (95% CI, 75%-100%) in detecting VT.

The TP, FP, FN, and TN values reported by Pascale et al are 0, 0, 3, and 2, respectively. GAST had a sensitivity of 0% (95% CI, 0%-71%) and specificity of 100% (95% CI, 16%-100%) in detecting VT.

The TP, FP, FN, and TN values reported by Yance et al are 0, 0, 2, and 13, respectively. GAST had a sensitivity of 0% (95% CI, 0%-84%) and specificity of 100% (95% CI, 75%-100%) in detecting VT.

The summary sensitivity for GAST is 10% (95% CI, 1.4%-46.7%) and the summary specificity is 100% (95% CI, 0%-100%). Out of 100 women with PH, GAST will fail to detect VT in 90 (95% CI, 53-99) women. Out of 100 women without PH, GAST will falsely detect VT in 0 (95% CI, 0-100) women. The summary negative likelihood ratio is 0.9 (95% CI, 0.714-1.086).

The TP, FP, FN, and TN values reported by Bricaire et al are 6, 0, 0, and 10 respectively. SOAVC had a sensitivity of 100% (95% CI, 54%-100%) and specificity of 100% (95% CI, 69%-100%) in detecting VT.

Kaltsas et al had 5 indeterminate cases in their study because 4-vessel cannulation failed. Based on a best-case scenario where all the unilateral OPG and APG correctly lateralizes the VT, the TP, FP, FN, and TN values will be 8, 5, 0, and 3 respectively, and the sensitivity will be 100% (95% CI, 63%-100%) and specificity will be 38% (95% CI, 9%-76%). Based on a worst-case scenario where all the unilateral OPG and APG lateralized VT incorrectly, the TP, FP, FN, and TN values will be 3, 7, 5, and 1 respectively, and the sensitivity will be 38% (95% CI, 9%-76%) and specificity will be 13% (95% CI, 0%-53%).

The TP, FP, FN, and TN values reported by Sörensen et al are 6, 0, 0, and 68 respectively. SOAVC had a sensitivity of 100% (95% CI, 54%-100%) and specificity of 100% (95% CI, 95%-100%) in detecting VT.

The summary sensitivity for SOAVC in the best-case scenario is 100% (95% CI, 0%-100%) and the summary specificity is 100% (95% CI, 3%-100%). Out of 100 women with PH, SOAVC will fail to detect VT in 0 (95% CI, 0-100) women. Out of 100 women without PH, SOAVC will falsely detect VT in 0 (95% CI, 0-97) women. The summary positive likelihood ratio is 12 216.53 (95% CI, –175 765 to 200 197.7) and the summary negative likelihood ratio is 0 (95% CI, 0-0). At a pretest probability of 0.2%, the posttest probability of a positive test is 0.961 (95% CI, 0.998-1.003).

The summary sensitivity for SOAVC in the worst-case scenario is 100% (95% CI, 17%-100%) and the summary specificity is 100% (95% CI, 9%-100%). Out of 100 women with PH, SOAVC will fail to detect VT in 0 (95% CI, 0–83) women. Out of 100 women without PH, SOAVC will falsely detect VT in 0 (95% CI, 0-91) women. The summary positive likelihood ratio is 74 480.42 (95% CI, –933 229 to 1 082 190) and the summary negative likelihood ratio is 0 (95% CI, –0.003 to 0.004). At a pretest probability of 0.2% [87, 88], the posttest probability of a positive test is 0.993 (95% CI, 1.000-1.001).

The forest plots for GAST and SOAVC are shown in Fig. 2 (best-case scenario) and Fig. 3 (worst-case scenario). The HSROCs for GAST versus SOAVC are shown in Fig. 4 (best-case scenario) and Fig. 5 (worst-case scenario). Table 2 shows the summary estimates for GAST and SOAVC.

Discussion

Summary of Main Results

The summary sensitivity of GAST is 10% and that for SOAVC is 100%. Both tests have 100% specificity. However, due to the small numbers of patients and studies, the 95% CI for all estimates are wide.

Strengths of This Study

This is the first systematic review on the diagnostic accuracy of GAST and SOAVC in identifying the source of androgen secretion in PH. There is no Cochrane review on this topic.

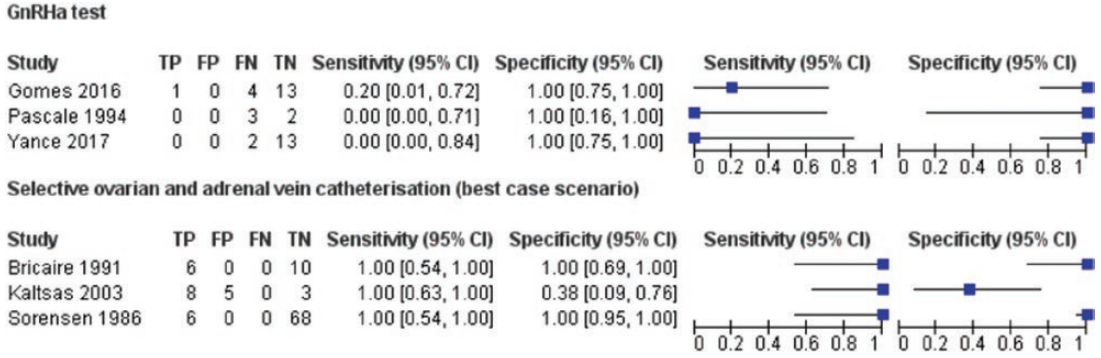

Figure 2. Forest plot: GAST versus SOAVC (best-case scenario) [13, 17, 18, 25-27].

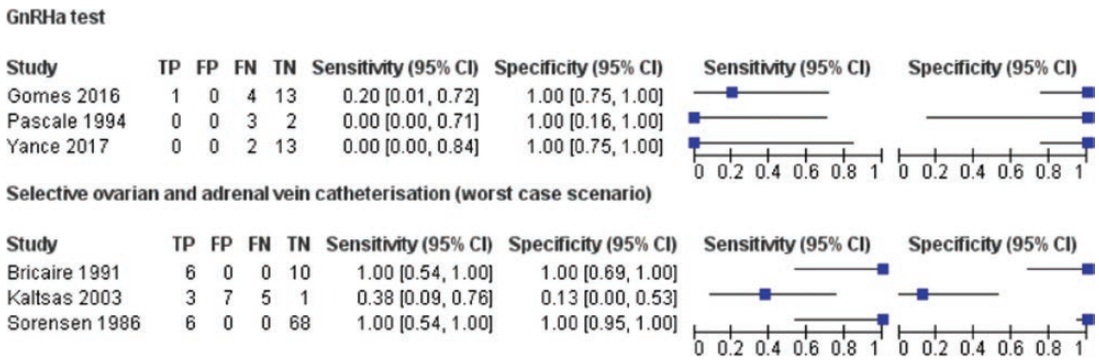

Figure 3. Forest plot: GAST versus SOAVC (worst-case scenario) [13, 17, 18, 25-27].

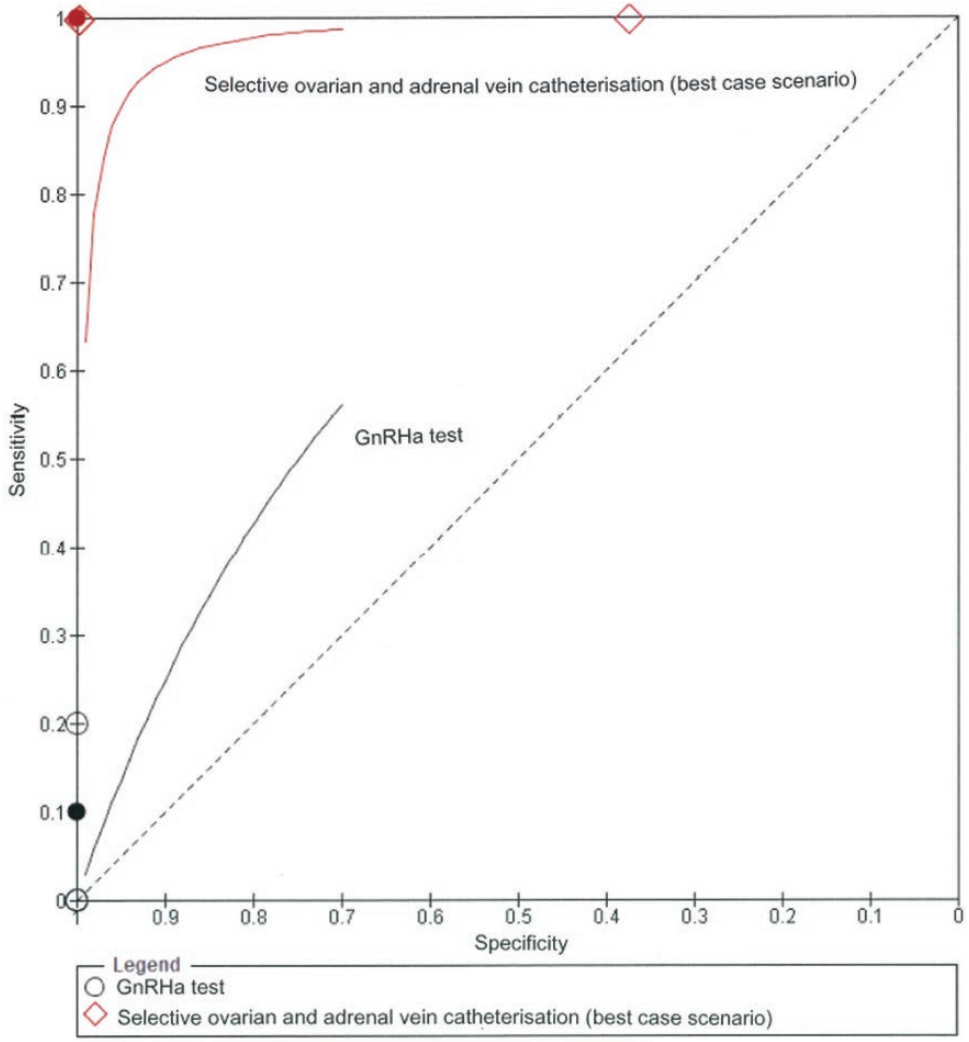

Figure 4. HSROC: GAST versus SOAVC (best-case scenario) [13, 17, 18, 25-27].

An extensive search of multiple databases was performed and the risk of errors in study selection and data extraction is reduced as 2 reviewers independently reviewed the articles. The use of HSROC method allows combination of different thresholds used for diagnosing PH by the different assays and it also allows comparison of ROCs of the various androgen assays.

Weaknesses of This Study

Most of the included studies are of poor methodological quality and are at high risk for bias based on the QUADAS-2 tool. Heterogeneity arising from the lack of standardization of the index tests and reference standards may undermine the comparison between the index tests. The findings of this study may not be valid in centers that conduct the index tests differently.

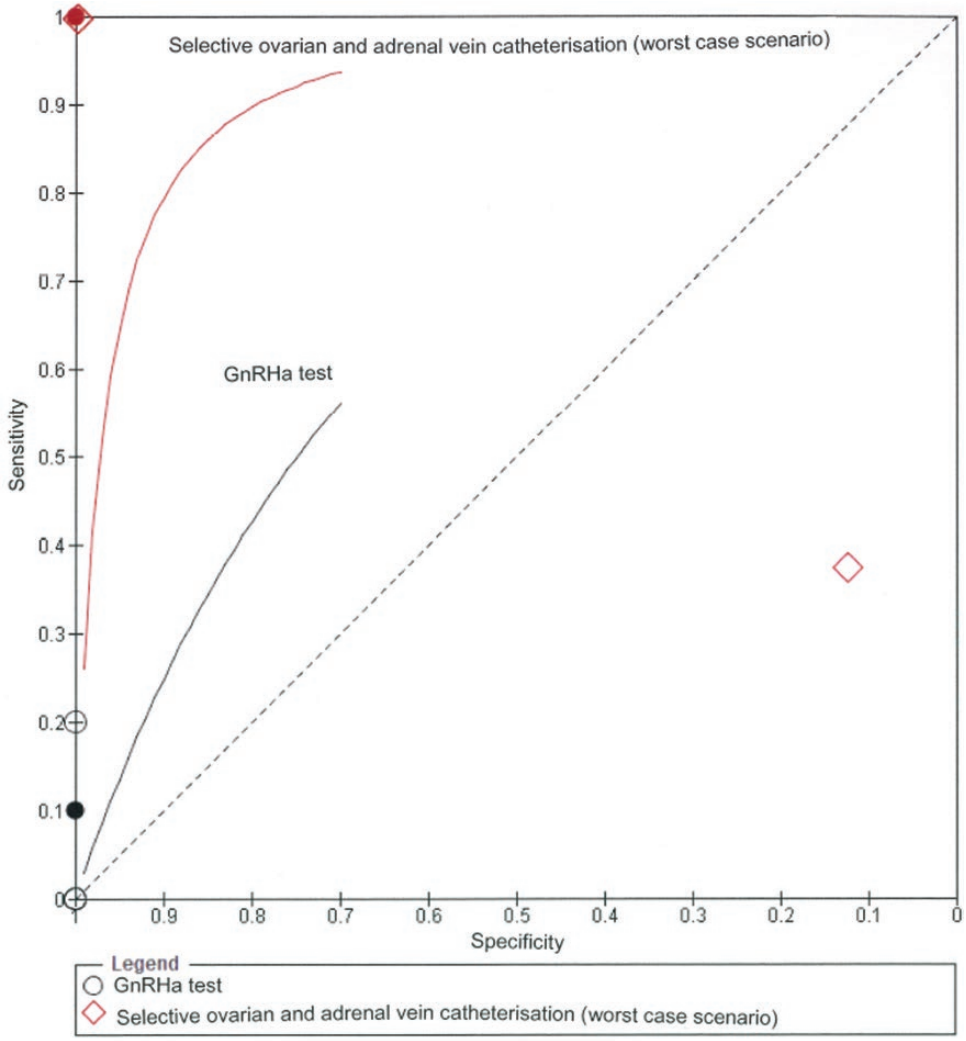

Figure 5. HSROC: GAST versus SOAVC (worst-case scenario) [13, 17, 18, 25-27].

Table 2. Summary Estimates

Study	Summary sensitivity	Summary specificity	Summary positive likelihood ratio	Summary negative likelihood ratio
GAST with testosterone suppression	10% (95% CI, 1.1%-46.7%)	100% (95% CI, 0%-100%)	- infinity	0.9 (95% CI, 0.714-1.086)
SOAVC (Best-case scenario)	100% (95% CI, 0%-100%)	100% (95% CI, 0.3%-100%)	12 216.53 (95% CI, −175 765 to 200 197.7)	0 (95% CI, 0-0)
SOAVC (Worst-case scenario)	100% (95% CI, 1.7%-100%)	100% (95% CI, 9%-100%)	74 480.42 (95% CI, −933 229 to 1 082 190)	0 (95% CI, −0.003 to 0.004)

Abbreviations: GAST, GnRH analogue stimulation test; SOAVC, selective ovarian and adrenal vein catheterization.

The small number of included studies led to low power in the summary estimates so differences between the index tests may not be detected. The summary estimates are imprecise so the findings of this meta-analysis must be interpreted with caution. Subgroup analysis could not be performed on postmenopausal subjects so the results of this meta-analysis may not be extrapolated to postmenopausal women.

Applicability of Findings

The studies were all conducted in tertiary referral centers so the findings may not apply to general settings. A single radiologist performed SOAVC over many years for most of the studies so the findings may not apply to inexperienced radiologists. The latest studies were done in 2003 and improvements in biochemical and radiological investigations since

2003 may invalidate the comparisons in this meta-analysis. As this is the only meta-analysis on this topic, further studies are needed to determine the reproducibility of our results.

Conclusions

Implications for Practice

There is limited evidence on the use of GAST and SOAVC in localizing VT in PH.

Implications for Research

Properly conducted diagnostic test accuracy studies on GAST and SOAVC in postmenopausal women are needed. Investigators should report the TP FP, FN, and TN values such that sensitivity and specificity of the tests can be compared. Researchers should standardize the diagnostic criteria for PH so that index tests can be compared against standardized reference standards.

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Author Contributions: Eng-Loon Tng designed and drafted the manuscript. Eng-Loon Tng and Jeanne May May Tan conducted literature searches; performed screening of titles, abstracts, and full-text articles; extracted data; conducted analysis; and wrote the review.

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Additional Information

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Disclosure Summary: Eng-Loon Tng and Jeanne May May Tan have no conflicts of interest to declare.

Data Availability: Some or all data generated or analyzed during this study are included in this published article or in the data repository listed [24].

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