Investigation of polycystic ovarian syndrome: variation in practice and impact on the speed of diagnosis

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Objective **Accurate diagnosis of polycystic ovarian syndrome (PCOS) enables clinical interventions/ cardiometabolic risk factor management. Diagnosis can take over 2 years and multiple clinician contacts. We examined patterns of PCOS-associated biochemical investigations following initial consultation prior to pelvic ultrasound scan (USS).**

Methods **We determined in 206 women (i) the range of different biochemical test panels used in the diagnosis of PCOS in primary/secondary care prior to USS relative to national guidance in the UK and (ii) the relation between testing patterns and time to USS to highlight potential delays introduced by inappropriate testing.**

Results **In these 206 women, 47 different test combinations were requested at initial venepuncture; only 7 (3%) had the test panel suggested in UK guidance (follicle-stimulating hormone/luteinizing hormone/ testosterone/sex hormone-binding globulin/prolactin). The number of tests performed prior to USS varied from one test to all seven tests. There was an inverse relation between the number of biochemistry tests requested at initial venepuncture episode and 'time to scan'. Those who had <3 tests had a significantly longer time from first request to USS (median 70 days) than those with 3–7 tests (median 40 days; *P*=0.002). One venepuncture episode prior to USS was associated with shorter 'time to scan' (median 29 days) than those with 2–4 episodes (median 255 days; *P*<0.001).**

Conclusion **There was no identifiable pattern to biochemical investigations requested as part of the initial diagnostic evaluation in women with suspected PCOS. We recommend standardization of the initial biochemical panel of analytes for PCOS workup, with incorporation into hospital/general practice ordering software systems. *Cardiovasc Endocrinol Metab* XXX: 000–000 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Polycystic ovarian syndrome (PCOS) is thought to be the most common endocrine disorder in women of reproductive age worldwide, affecting 8–10% of this group, including women living in South Asia [1–4]. It has a heterogeneous clinical presentation, including menstrual disturbances, infertility, overweight/obesity and hirsutism. Women with PCOS are at a higher risk of developing type-2 diabetes and have increased cardiovascular risk factors as compared to age and weight-matched women without PCOS. [5]. Accurate diagnosis is important for early intervention to prevent future adverse health outcomes and to initiate appropriate treatment. However, a recent study showed that it can take over 2 years and for the women to see more than three different healthcare professionals before the accurate diagnosis of PCOS is made [6].

Currently, there is no international consensus regarding the diagnostic criteria and the prevalence rate estimates differ depending on the diagnostic criteria used [1]. The American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society have jointly published best practices for evaluating and treating PCOS [2,3]. These bodies still use the 1990 National Institutes of Health (NIH) criteria (no ovarian scan). In the UK, the Rotterdam criteria are applied with PCOS diagnosed when two out of the following three criteria are met: chronic anovulation, polycystic ovaries (PCO), or clinical or biochemical evidence of hyperandrogenism [1].

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Although the laboratory investigation of PCOS and its associated symptoms is clearly important, there is uncertainty among clinicians around which tests should be requested, and in what order, prior to ultrasound scanning. The webpage of 'Lab Tests Online UK' lists a wide range of possible investigations that may be performed [7], but does not specify which ones are recommended in specific situations. In the UK, the National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries also provide guidance for clinicians on which tests to perform [8], on the basis of the guidelines from the Royal College of Obstetricians and Gynecologists [9]. Our observations of clinical practice suggest that these are not always followed.

We previously showed that there is a wide disparity in the diagnostic investigations requested for PCOS between different general practices, with the practice also influenced by the demographics of the population [10,11]. Furthermore, it is clear that the wider clinical community is often uncertain about which test to request.

The objective of this study was to determine (i) the range of different biochemical test panels used in the diagnosis of PCOS in primary or secondary care prior to ultrasound scanning relative to NICE guidance and (ii) the relation between testing patterns with time to ultrasound scan with a view to highlighting the potential delay introduced by inappropriate testing.

Methods

In order to identify women who had been investigated for PCOS using pelvic ultrasound scan (USS), the radiology database at a single referral center, the University Hospital of North Midlands, a large Acute Trust covering Staffordshire, UK, was searched over a 26-month period. The search terms were PCOS, PCOM, PCO, multicystic and infertility in either the clinical details or the results sections of radiology reports.

Data were then collected from the Laboratory Information and Management System on the clinical biochemistry investigations performed in these women during the 2 years prior to the date of their pelvic ultrasound imaging. These were tests frequently requested by a range of primary and secondary care clinicians for diagnostic purposes in PCOS, specifically: luteinizing hormone, follicle-stimulating hormone (FSH), estradiol, progesterone, prolactin, total testosterone and sex hormone-binding globulin (SHBG). From this, we identified a cohort of 206 women who underwent pelvic USS and had at least one of these tests during this period. As a service evaluation project, this project was exempt from requiring ethical approval.

Statistical analyses were performed using Stata (Release 14. StataCorp LLC, College Station, Texas, USA). Kaplan–Meier plots and Cox's proportional hazards regression were used to examine time to scan event data.

Results

Assessment of the pattern of relevant biochemical tests (FSH, luteinizing hormone, estradiol, testosterone, prolactin, SHBG and progesterone) requested by primary and secondary care clinicians showed that various combinations (panels) of these biochemical investigations were requested at the initial consultation, such that 47 different permutations were conducted as part of the diagnostic evaluation (Table 1).

FSH was the most commonly requested test and was present in 34/47 test panels (accounting for 179/206 requests). The top five most common panel of initial tests were: FSH, luteinizing hormone, testosterone and prolactin (15%, $n = 30$), FSH, luteinizing hormone and testosterone (14%, $n = 29$), FSH and luteinizing hormone (10%, $n = 21$), FSH, luteinizing hormone and prolactin (8%, $n = 16$), and FSH, luteinizing hormone, estradiol, progesterone, prolactin and testosterone (6%, $n = 13$). Only seven women (3%) had the initial panel suggested in NICE guidance (panel 7: FSH, luteinizing hormone, testosterone, SHBG and prolactin), with a further three women having these plus other tests [two with added estradiol (panel 19), one with added estradiol and progesterone (panel 27)]. SHBG was the most commonly missed test, being present in only 10 of the 47 panels (Table 1).

The number of tests performed prior to ultrasound scanning varied from a single test to the full panel of seven tests (Table 1). Examining the data, there appeared to be an inverse relationship between the number of biochemistry tests requested at the initial venepuncture episode and 'time to scan'. Those who had less than three tests had a significantly longer time from the first request to pelvic USS (median time 70 days) than those with three to seven tests (median time 40 days; $P = 0.002$; HR = 1.6; 95% CI, 1.2–2.2; Fig. 1a).

We also showed that women had up to four venepuncture episodes in the 2 years prior to their pelvic USS: 159 with a single venepuncture, 36 had two, 9 had three and 2 had four venepuncture episodes. One venepuncture episode was associated with a significantly shorter 'time to scan' (median time 29 days) than those with more than one venepuncture episode (median time 255 days; $P < 0.001$; HR = 1.6; 95% CI, 2.3–4.6; Fig. 1b).

Discussion

Our study demonstrates the wide variation in the biochemical investigations requested as part of the diagnostic evaluation for PCOS prior to the sonographic assessment of the ovarian morphology when pelvic USS is performed. This means that management of PCOS with such measures as dietary intervention and metformin may be delayed by months, with a knock-on effect in terms of cardiometabolic health and cardiometabolic risk management in the longer term.

Only 7% of cases had the initial panel of tests suggested in UK national guidance (FSH, luteinizing hormone,

Table 1 Panels of tests performed prior to ultrasound scan for suspected PCOS

Test panel number	FSH	Luteinizing hormone	Testosterone	SHBG	Prolactin	Oestradiol	Progesterone	Total tests in panel	Total requests for panel
1	X	X	X		X			4	30
2	X	X	X					3	29
3	X	X						2	21
4	X	X			X			3	16
5	X	X	X		X	X	X	6	13
6					X			1	8
7	**X**	**X**	**X**	**X**	**X**			**5**	**7**
8	X	X	X			X		4	6
9							X	1	6
10	X	X	X		X		X	5	5
11	X				X			2	5
12	X	X	X		X	X		5	4
13	X	X					X	3	4
14	X	X	X				X	4	3
15	X	X				X		3	3
16	X	X				X	X	4	3
17	X		X		X			3	3
18	X		X					2	3
19	**X**	**X**	**X**	**X**	**X**	**X**		**6**	**2**
20	X	X	X	X				4	2
21	X	X			X	X		4	2
22	X	X			X	X	X	5	2
23	X		X					2	2
24	X							1	2
25			X	X				2	2
26			X					1	2
27	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**7**	**1**
28	X	X	X	X		X		5	1
29	X	X	X			X	X	5	1
30	X	X		X				3	1
31	X	X		X		X		4	1
32	X	X			X		X	4	1
33	X		X		X		X	4	1
34	X		X		X	X		4	1
35	X		X			X		3	1
36	X			X				2	1
37	X						X	2	1
38	X					X		2	1
39		X	X			X	X	4	1
40		X	X			X		3	1
41		X			X		X	3	1
42			X	X		X		3	1
43			X		X	X	X	4	1
44			X		X	X		3	1
45			X		X			2	1
46					X	X	X	3	1
47					X	X		2	1
Total panels	**34**	**26**	**27**	**10**	**22**	**22**	**16**		

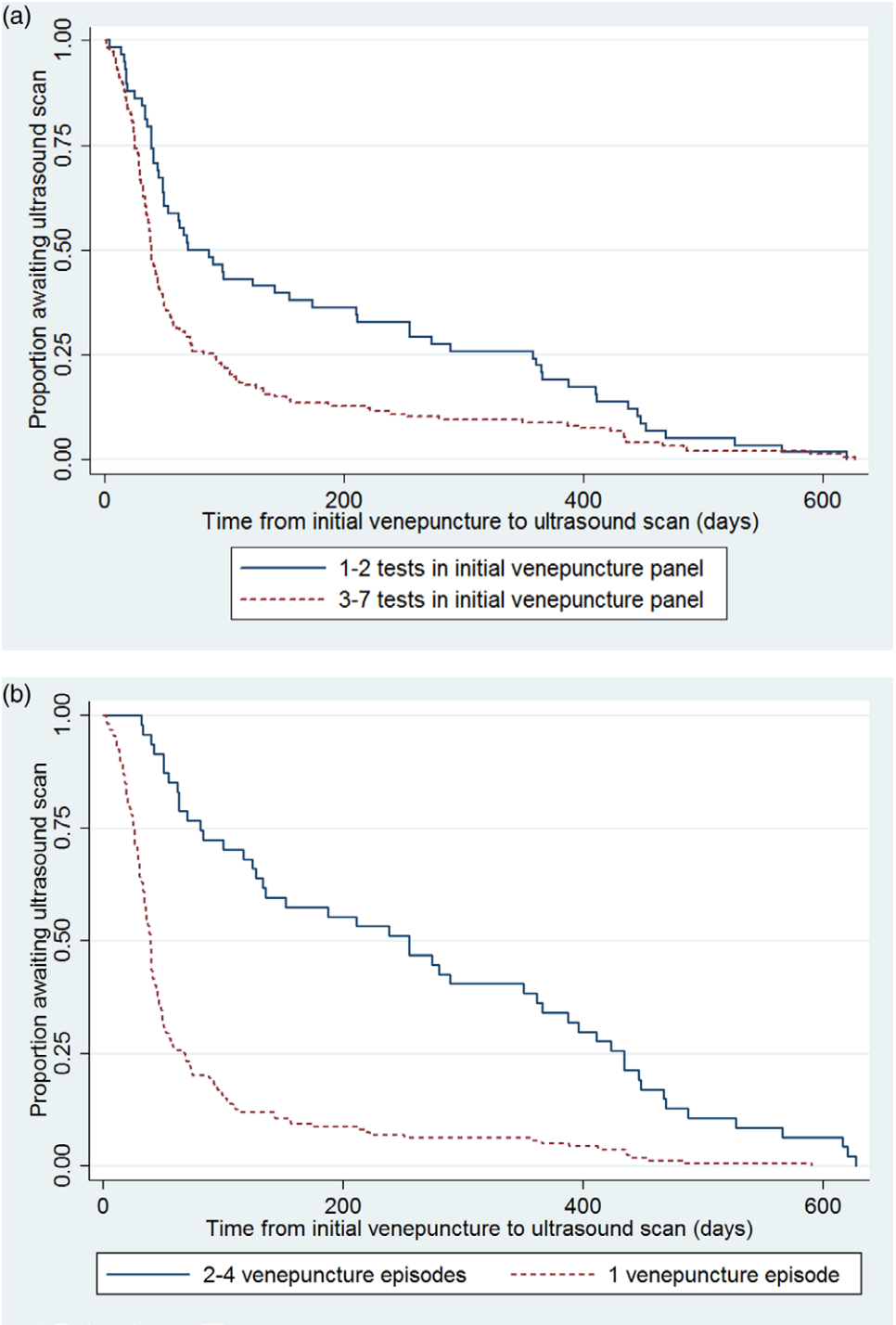
Panels containing the tests recommended in the guidance are shown in bold.
FSH, follicle-stimulating hormone; SHBG, sex hormone-binding globulin.

testosterone, SHBG and prolactin). Furthermore, the number of tests performed prior to USS was linked to the time taken to arrange the USS scan; requests comprising fewer than three tests were associated with a longer delay before pelvic USS was performed. Similarly, those cases that had only one venepuncture episode had a significantly shorter 'time to scan' than those with more than two to four venepuncture episodes. Hence, our data illustrate the need for appropriate test requesting, with the availability of clear guidance for any clinician who might see such patients, in order to ensure timely follow-up investigations.

Previously, we showed a wide variation in patterns of investigations in PCO/PCOS in UK primary care prior to general practice-coded cases with a diagnosis of PCOS, where the recommended endocrine tests were not as frequently requested as expected [11]. This is consistent with the findings of the current study on testing prior to ultrasound scanning, though this study included requests from both primary and secondary care, indicating that the challenge in appropriate requesting is more widespread than that in general practice. We are not aware of any other studies which have investigated such variability in testing in women being investigated for symptoms associated with PCOS. We did not include measurement of lipid or glycaemic status as this has been covered in previous papers and are not currently part of the diagnostic criteria for PCOS.

The observation of 47 different permutations in testing panels suggests that clinicians are unclear on what tests to perform in women with symptoms associated with PCOS. This is particularly highlighted by the lack of requesting of SHBG when investigating PCOS, despite its recommendation in guidelines from the Royal College

Fig. 1



Kaplan–Meier survival plots showing an association between time to ultrasound scan and (a) number of tests at initial venepuncture episode and (b) number of venepuncture episodes.

of Obstetricians and Gynaecologists, National Institute for Health and Care Excellence and other international guidance [2,3,11,12]. Indeed, SHBG was only included in 19 (9.2%) out of the 206 requests. We do recognize, however, that some of the variations may reflect the different presenting signs and symptoms associated with PCOS. Symptoms such as infertility may well prompt testing of estradiol and progesterone. In these cases, testosterone and SHBG as tests more relevant in the presence of hirsutism/acne might not be seen as a first-line test, though the disparity between testosterone and SHBG requesting in our study suggests that investigation for other causes

is not the sole cause of the variation. Furthermore, we and others have described the link between a low SHBG and insulin resistance which is frequently a feature of PCOS [13].

We determined that laboratory testing is a factor linked to delay in diagnosis in women with PCOS. However, most requests were made in general practice, as a significant minority (12.6%) were requested by secondary care clinicians. The varied and yet nonspecific signs and symptoms with which women with PCOS present make the selection of appropriate tests by nonspecialists challenging [12].

Our findings imply that there may be a benefit in standardizing the approach to the investigation of women with symptoms suggestive of PCOS across primary and secondary care. There have been numerous attempts to improve the appropriateness of laboratory requesting [14,15]. One such approach might be the generation of specific panels of tests, linked to PCOS and/or its associated symptoms (e.g. acne, amenorrhea, hirsutism, infertility and hair loss), accessible to clinicians via electronic test ordering systems. Test request panels have the benefit of improving standardization and/or reducing inappropriate testing [16], but studies indicate that these need to be managed carefully in order to prevent excessive over-ordering of tests [17]. An agreed panel of tests at a single venepuncture would seem a sensible option.

The strength of this study lies in the comprehensive evaluation of a defined population of women with known USS ovarian morphology and their biochemical investigations, as requested by the clinicians who saw them, prior to the scan. On the other hand, this study is also limited by this selected group where all women underwent pelvic USS. As such, we do not have any data on women who were diagnosed with PCOS based on clinical presentation and biochemical investigations without any sonographic evaluation. Another limitation is that we did not have detailed information about comorbidities, medications and the day of the menstrual cycle when the investigation was performed.

In summary, there was no identifiable pattern to the biochemical investigations requested as part of the initial diagnostic evaluation in women with suspected PCOS. We recommend standardization of the initial biochemical panel of analytes for PCOS workup, with incorporation into hospital and general practice ordering software systems. This should improve efficiency and diagnostic yield and, above all, will be very helpful to the doctors and nurses who perform the evaluation of PCOS in the everyday clinical setting, so that treatment can be started in a timely manner.

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Conflicts of interest

There are no conflicts of interest.

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