Anti-Mullerian Hormone (AMH) testing prior to endometrioma surgery in reproductive age women not seeking assisted fertility care: a cross-sectional survey of current clinical practice in the United Kingdom

Sarah Wali*, Akanksha Garg, Kate Maclaran, Amer Raza, Robert Richardson

Department of Obstetrics and Gynaecology, Chelsea and Westminster Hospital, 369 Fulham Road, London, SW10 9NH, United Kingdom

**Author for correspondence: sarah.wali@doctors.org.uk*

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Abstract

Objective: To evaluate current practice amongst gynaecologists in the United Kingdom with regards to measuring serum Anti-Mullerian Hormone (AMH) prior to endometriod cystectomy in women who are not seeking assisted reproduction.

Study Design: Cross-sectional survey. Practising gynaecologists (n=121) from 67 endometriosis centres across the United Kingdom were sent an online survey. The main outcome of interest was to determine the proportion of gynaecologists who have access to AMH testing, perform pre and post-operative AMH testing in National Health Service (NHS) and Private practice, and considerations of other patient risk factors for testing. Both quantitative and qualitative data analysis was conducted where appropriate.

Results: 43% (n=52) responses were received from consultants working at 58% (n=39) British Society of Gynaecological Endoscopy (BSGE) endometriosis centres across the UK. 79% (n=41) of consultants routinely counsel patients preoperatively regarding the impact of endometrioma surgery on ovarian reserve, whilst 17% (n=9) of consultants will counsel patients if their family is incomplete. 4% (n=2) of consultant's report not counselling patients regarding the above. 50% (n=26), 21% (n=11) and 21% (n=11) reported preoperative AMH testing to be desirable, mandatory (important medico-legally) or not useful (not evidenced based) respectively. Our results showed an association between access to AMH testing and its routine use; 69% (n= 35) with access to testing will routinely test preoperatively.

Conclusion: There is widespread pre and postoperative AMH testing in this patient group in NHS and Private practice. If there is access to the test, consultants are likely to consider it as mandatory or desirable ($p<.05$). Only 21% consultants view this test as not evidenced or useful. The use of AMH is strictly in the management of the infertile woman as levels in women without infertility do not correlate with fertility potential or the time to pregnancy. AMH should not be used to predict fertility or onset of menopause in women not diagnosed with infertility.

Keywords: Anti-Müllerian Hormone (AMH) • current practice • endometrioma surgery • ovarian cystectomy • fertility • endometriosis

Introduction

Decreased Ovarian Reserve (DOR) refers to reproductive age women with regular menses but reduced fecundity (natural or stimulated) compared with similar aged women [1]. It is the most common reason leading to women undergoing Assisted Reproductive Technology (ART) [2]. Anti-Mullerian Hormone (AMH) is secreted by granulosa cells in small preantral and early antral follicles and reflects the size of the primordial follicular pool [3]. It is an established marker of ovarian reserve used in fertility management to predict poor ovarian response and low values are used to guide exclusion criteria for women seeking ART [4]. Recent meta-analyses suggested measuring serum AMH has weak predictive value in natural clinical

pregnancies [5] but evidence for its use to predict live birth is limited. Furthermore, serum AMH levels in women without infertility (defined as difficulty conceiving after 1 year of regular intercourse) [6] have not been shown to correlate with either future fertility potential or predict spontaneous conception [5]. Therefore, routine AMH testing is not recommended as a fertility prediction tool in women without a diagnosis of infertility [7,8].

Endometriosis is a common chronic condition affecting 10% of women of reproductive age and up to 50% of infertile women. [9] In its milder form, inflammatory mechanisms create a cytotoxic environment for gametes and embryos, whilst more severe endometriosis results in adhesions to the fallopian tubes and the presence of endometriomas [10].

Despite having more adverse effects on ovarian reserve, current European Society of Human Reproduction and Embryology (ESHRE) guidance on endometriosis recommends ovarian cystectomy as first line treatment for symptomatic endometriomas [11,12]. Cystectomy is considered superior to drainage, coagulation or vaporisation alone due to a reduced risk of recurrence, and that subsequent surgeries are more harmful to ovarian reserve than a successful primary surgery [13]. However, the ESHRE Fertility preservation guidelines does not specifically distinguish between the counselling and management of benign and malignant ovarian pathologies, suggesting that preoperative personalised counselling, including the opportunity to freeze eggs, should be considered [14].

Standardised pre-operative ovarian reserve assessment is currently not recommended by ESHRE [13] when counselling women for ovarian cystectomy, despite the established surgical risk of loss of follicle reservoir and increased risk of premature ovarian failure [15]. The American Committee of Gynecologic practice recommends ovarian reserve testing in women at high risk for DOR, including women with endometriosis. This allows initiation of fertility evaluation and an opportunity to counsel women regarding potential shorter windows of conception [1,16].

The current lack of evidence to guide both the best surgical approach to endometriotic cystectomy as well as the value of pre-operative ovarian reserve assessment has resulted in varying clinical practice. We therefore aimed to evaluate current clinical practice of pre-operative AMH testing in women undergoing endometrioma surgery who are not seeking ART within the United Kingdom. Women seeking ART were excluded as they routinely receive AMH testing as part of their work up to predict response to ovarian stimulation [17]. Currently ESHRE guidance recommends that if ART is planned, the prospect of success is not increased by prior endometrioma removal regardless of the size of the endometrioma, and surgery may in fact have a negative impact on the ovarian reserve as evidenced by the need for higher dose of FSH for ovarian stimulation. Many clinicians would recommend symptomatic women to proceed with ART prior to endometrioma surgery if the woman's main goal is fertility [13].

Method

Ovarian cystectomies for endometriomas are routinely performed by gynaecologists throughout the United Kingdom. The British Society of Gynaecological Endoscopy (BSGE) endometriosis centre database consists of a comprehensive list of surgeons accredited for compex endometriosis surgery. These surgeons operate on endometriomas routinely and at a higher volume compared to general gynaecologists. At the time of this study, 121 practising accredited consultants from 67 registered endometriosis centres were included.

We conducted a cross-sectional survey using an electronic SurveyMonkey® invitation. The survey consisted of 10 closed-ended questions to establish the respondents' demographics, pre and post-operative management, counselling of patients, and the rationale behind the decision making. free text opportunity for further comments was provided to delineate variables in the decision making process that were not accounted for through closed questioning. The survey allowed responses for 6 weeks from 1st November 2021, and follow-up reminders were sent at two-week intervals.

Responses from individuals were collated on Microsoft Excel. Descriptive statistics were used to present results as frequency counts and percentages (%) for categorical variables. Statistical analysis was conducted using excel. As per the Health Research Authority (HRA) guidelines, ethical approval was not required.

Results and Discussion

This is the one of the first cross-sectional studies to evaluate current UK practice of AMH testing in women undergoing endometrioma surgery and not seeking ART. The results of this survey provide an understanding of practice to

ignite professional discussion and attempt to standardise practices.

Out of the 121 BSGE accredited consultants, 43% (n=52) responded, representing 58% (n=39) of BSGE endometriosis Centre's (**TABLE 1**). The results of each question are presented in **TABLE 1**.

TABLE 1. The 10 questions included in the survey are presented here, along with answer options and the results (% and n values).

Question	Answer Options	Response % (n)
Q1. Do you work at a BSGE endometriosis centre?	Yes	100% (52)
Q2. When you see reproductive age women with endometriomas do you routinely counsel them pre-operatively regarding the impact of endometrioma surgery on ovarian reserve?	Yes	79% (41)
	No	4% (2)
	Only if family is not complete	17% (9)
Q3. Do you consider AMH levels pre-operatively as:	Desirable	50% (26)
	Mandatory / important medico-legally	21% (11)
	Not evidence based	13% (7)
	Not useful	8% (4)
	I use another marker of ovarian reserve (please specify)	8% (4)
	Answers include: AFC, Hormone Profile	
Q4. Do you have access to AMH level testing for reproductive age women not seeking assisted fertility care in your NHS practice?	Yes	67% (35)
	No	33% (17)
Q5. Do you routinely request an AMH level prior to endometrioma surgery for reproductive age women not seeking assisted fertility care in your NHS practice?	Yes	46% (24)
	No	36%, (19)
	Not funded/ no access	17% (9)
Q6. Do you routinely request an AMH level prior to endometrioma surgery for reproductive age women not seeking assisted fertility care in your Private practice?	Yes	37% (19)
	No	31% (16)
	I don't do private cystectomy surgery	33% (17)
Q7. If not routinely requested for women not seeking assisted reproduction, would you consider AMH level testing in certain situations (tick all relevant)	Previous endometrioma surgery (recurrent endometriomas)	50% (26)
	Single ovary (previous oophorectomy)	50% (26)
	Patient request	48% (25)
	Presence of bilateral endometriomas	46% (24)
	I routinely request AMH for these patients	44% (23)
	Nulliparous and ≥35years	40% (21)
	Large cyst (≥6cm)	35% (18)
	Stage 4 endometriosis	25% (13)
	I would not request AMH outside assisted fertility setting	17% (9)
	Other (please specify)	8% (4)
	Answers include:	
	- AMH for those who wish to have family (spont or assisted) after cystectomy if no prior ovarian surgery and before surgery if prior ovarian cystectomy for endometrioma	
	- Regardless of parity, for women desiring fertility aged above 35	
	- Only if they have future desires to be pregnant	
	- No NHS practice	
Q8. If you perform a pre-operative AMH level do you repeat it post-operatively in your NHS/Private practice?	Yes whenever possible	27%
	No	46%
	I don't do preoperative AMH level	27%
	If you do post-operative AMH when do you time this? (weeks/ months)	
	Answers include:	
	- 3-4 months	
	- 3 months but depends on individual situation	
	- After 6 months	
	- 12 weeks	
	- 3-6 months	
	- 3 months	
Q9. What is your grade?	Consultant / Associate specialist / post CCT	100%

Q10. Which region do you work in?	London North West	13%
	London North Central and East	17%
	London South	10%
	East of England	10%
	East Midlands	2%
	Kent Surrey Sussex	8%
	Mersey	2%
	North Western	6%
	Northern	6%
	Northern Ireland	0%
	Oxford (Thames Valley)	4%
	Scotland	4%
	Severn	2%
	Southwest Peninsula	8%
	Wales	2%
	Wessex	2%
	West Midlands	4%
	Yorkshire and the Humber	2%

The majority of gynaecologists (79%, n=41) routinely counsel patients regarding the impact of endometrioma surgery on fertility (Question 2). 17% (n=9) of gynaecologists counsel patients only if their family is incomplete. A very small proportion (4%, n=2) do not counsel at all. Good clinical practice would be to counsel all women of natural conception age of the potential impact of endometrioma surgery on their fertility [13]. This would facilitate informed decision making and allows the patient to prioritise their treatment goals.

Preoperative AMH testing is available to 67% (n=35) of respondents through their NHS practice (Question 4). Preoperative AMH testing is done by 46% (n=24) of respondents in NHS practice (Question 5) and 54% (n=19) in private practice (Question 6). The increased use of AMH testing in private practice could be due to greater accessibility and the flexibility to recommend investigations not listed in clinical guidelines [18]. However, those that do not request AMH in their private practice also do not request it in their NHS practice. This implies that it is the clinician's perception of the test's importance rather than its accessibility that influences practice.

McNemar's test was used to demonstrate that there is an association between having access to the test and routinely requesting (p=0.0026). Of the 35 that have access, 24 routinely requested serum levels. Consultants who do not have access to testing do not routinely request it **TABLE 2**.

AMH testing is perceived as desirable by 50% (n=26), mandatory by 21% (n=11) and not evidence based or useful by 21% (n=11). To further explore the relationship between access to testing and desirability, chi-squared statistical analysis was conducted (Table 3). There is a significant association (p=0.037) between having access to the test and the perceived desirability or usefulness of the test. Surgeons with access to testing are more likely to find the test desirable or mandatory, whilst those without access are more likely to find the test not evidenced or useful. Further research exploring why differing perceptions exist is necessary, including analysis of why and what factors drive surgeons' decision making.

Of those that do pre-op AMH testing, postoperative AMH is checked by 42% (10/24) in NHS practice and 53% (10/19) in Private practice, the timing of the testing is variable and answers range from 3 months to more than 6 months post operatively. In addition to the permanent effects of inadvertent excision of healthy ovarian stroma during cystectomy, proposed temporary mechanisms for postsurgical ovarian reserve decline include thermal damage, vascular injury and postoperative inflammatory response [19]. After ovarian injury, it takes up to 6 months for the 'recovery' and resumption of baseline folliculogenesis, and the development of prenatal and antral follicles from the primordial follicle pool. There is limited evidence evaluating the impact of cystectomy on ovarian reserve beyond the 6-month time point [19].

17% (n=9) would not perform AMH outside of an assisted fertility setting regardless of presence of additional risk factors for increased reduction in ovarian reserve (Question 7). There is a responsibility to think about the cost-effectiveness and the cost–benefit balance of an expensive preoperative test outside of national guidance. French guidelines recommend that reproductive age women should be informed

TABLE 2. The association between consultants having access to AMH testing compared with routine testing.

	Question 4		
Question 5	Access to AMH test (n)	No Access to AMH test (n)	Total (n)
Routinely request	24	0	24
Do not routinely request	11	17	28
Total	35	17	52 (Grand Total)

TABLE 3. The association between access to AMH testing and the perceived importance of the test.

		Question 4		
	Perception of importance of test	**Access to AMH test**	**No Access to AMH test**	**Totals**
Question 3	Mandatory / important medico-legally	10 (7.56) [0.79]	1 (3.44) [1.73]	11
	Desirable	19 (17.88) [0.07]	7 (8.12) [0.16]	26
	Not evidence based	3 (4.81) [0.68]	4 (2.19) [1.50]	7
	Not useful	1 (2.75) [1.11]	3 (1.25) [2.45]	4
	Totals	33	15	48*
(*4/52 used other markers of ovarian reserve and were not included in the calculation)				

of the potential impact on ovarian reserve and fertility preservation options before operating on any of the following: bilateral endometriomas > 3 cm, recurrent unilateral endometriomas, and endometrioma on a single ovary [20]. In case of a first and unilateral endometrioma > 3 cm, the guidelines recommend an individualised approach to counselling, taking age and ovarian reserve into account [20]. This raises the question as to whether guidelines should reconsider the value of AMH testing in this patient population.

In total, 27 PWD had a c-peptide response >200, and 315 had a response <200 pmol/l. All subjects with a c-peptide response >200 pmol/l were among the 307 subjects without FHD, whereas none of the 35 subjects with FHD had a meal stimulated c-peptide >200 pmol/l, p=0.048.

■ Subgroup analysis by geographical region

Analysis based on region of practice showed considerable heterogeneity in terms of counselling, perceived importance of AMH testing, availability within the NHS, and routine requesting within the NHS and private practice (Questions 2-6, **FIGURE 1**). This could be due to various reasons. Firstly, with the current evidence, there is a lack of a clear consensus as to whether AMH testing in such cases is clinically indicated. Secondly, it could be due to infrastructure, funding and resourcing differences between regions, resulting in varied clinical practice.

■ Clinical implication

Potential benefits of pre-operative AMH testing include guiding decision making regarding the preferred surgical approach to endometriotic cystectomy (excision vs drainage vs photovaporization vs 3 step procedure (drain, 3 months GnRH analogues, photovapourise)). The ablative approach with the carbon dioxide laser seems to be the surgical technique with the least impact on postoperative AMH levels and results in better pregnancy rates [19].

Additionally, in combination with female age, preoperative serum AMH testing can be used as a screening tool to identify women with endometriomas who are less likely to achieve pregnancy through ART [1]. A low preoperative AMH value may be important for women with endometriomas who are not actively trying to conceive but may want to in the future and may therefore wish to prioritise their fertility desires over endometrioma surgery [16].

It is prudent to also discuss the potential concerns with using AMH as a screening test in this patient population. The normal ranges for AMH vary in the literature, making it challenging to define set criteria clinically [21]. Furthermore, a low AMH level does not necessarily correlate with decreased natural fertility, and in young women, the prevalence of DOR is low. The probability that a young woman with low AMH truly has DOR is low, even if the sensitivity and specificity of AMH levels for ovarian reserve are high. Additionally, AMH levels do not represent the age appropriate quality of the oocytes. Therefore, in women who are not seeking fertility treatment / curious about their reproductive potential, AMH use for pre conception counselling may cause unnecessary fertility anxiety [5].

■ Strengths and limitations

The main strengths of this study is that all BSGE accredited gynaecology surgeons had the opportunity share their practice, ensuring

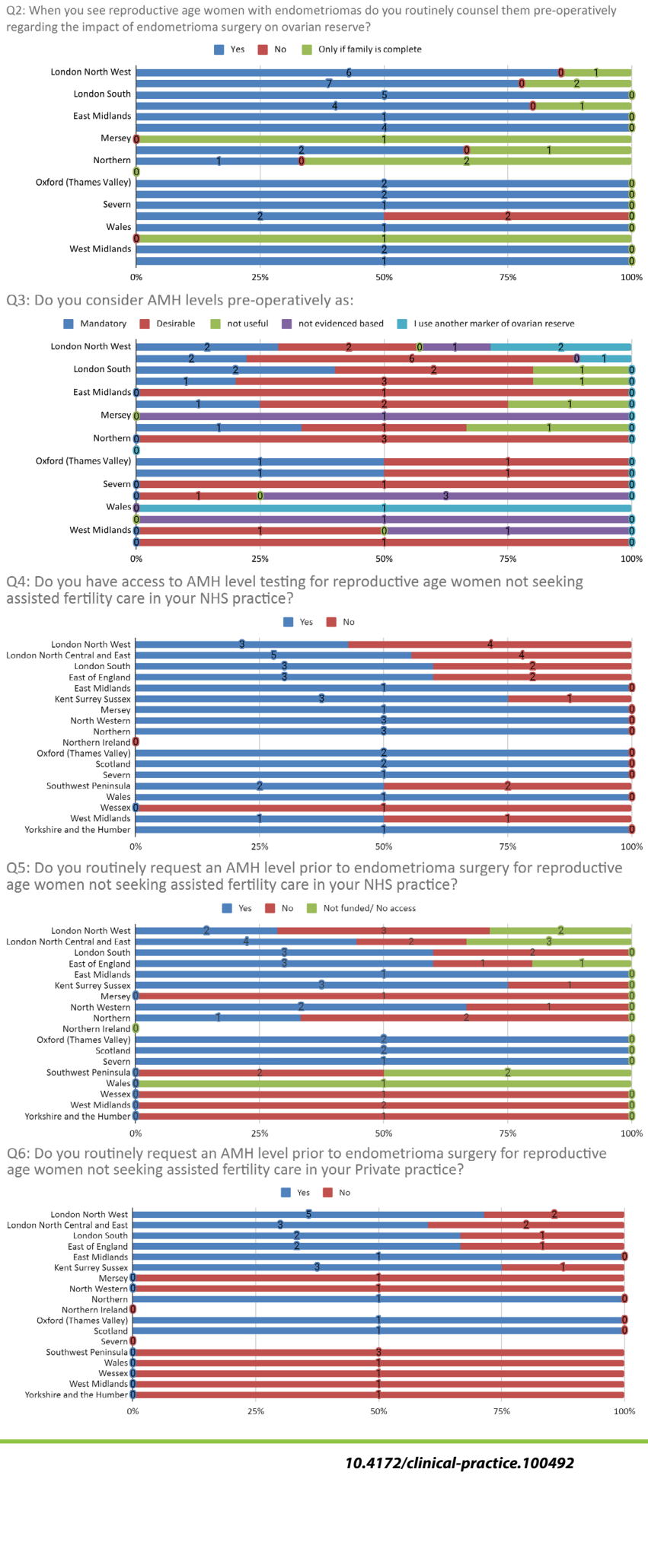

FIGURE 1. (ABCDE) Subgroup analysis by geographical location of respondents.

adequate coverage and allowing generalisability of findings. The limitations of this survey is that less than 50% of consultants responded, which could introduce a degree of bias.

Conclusion

There is insufficient evidence and lack of clear guidance regarding the use of AMH testing as a screening tool in reproductive age women who are not seeking fertility treatments but are undergoing endometrioma surgery. There is widespread pre/postoperative AMH testing in these patients within NHS and private practice, especially with access to testing.

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