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# The utility of anti-Müllerian hormone in women with chronic kidney disease, on haemodialysis and after kidney transplantation

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**KEY MESSAGE**

Anti-Müllerian hormone (AMH) is lower in young women with renal failure compared with age-matched healthy controls but not in those on haemodialysis. AMH decreases with age in women with renal failure in a similar manner to the general population. AMH may have a role as a marker of ovarian health in non-dialysis renal patients pursuing pregnancy.

A B S T R A C T

Women with renal disease have menstrual and gonadal dysfunction manifesting as hormonal imbalance. Anti-Müllerian hormone (AMH) is a potential measure of ovarian reserve. We examined circulating AMH concentrations in young women with renal failure, determined associations with clinical characteristics, and compared AMH with age-matched healthy individuals. AMH was measured in 77 women: 26 had chronic kidney disease (CKD), 26 were on haemodialysis (HD), and 25 had a kidney transplant. Random AMH levels were highest in women on HD [HD 2.9 (1.1–5.2), CKD 1.6 (0.7–2.2), transplant 1.5 (1.0–4.2) ng/ml]. On multiple linear regression, AMH was 53% higher [95% CI 0.20–0.98, $P = 0.002$] in women on HD and decreased by 20% per 5-year increase in age ($P < 0.001$). AMH was 43% lower in women with renal failure compared with 600 age-matched controls [1.7 (0.9–3.8) versus 3.0 (1.9–5.0) ng/ml, $P < 0.001$]; however, we found no difference in AMH between those on HD and healthy individuals [2.9 (1.1–5.2) versus 3.0 (1.9–5.0) ng/ml]. AMH may be a useful biomarker in female renal patients with non-dialysis dependent renal disease pursuing pregnancy. In contrast, AMH levels are higher in HD but unlikely to reflect ovarian reserve.



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## Introduction

Anti-Müllerian hormone (AMH) is a glycoprotein with a fundamental role in male sex differentiation. In women, AMH plays a critical role in folliculogenesis, with circulating levels directly reflecting the number of developing pre-antral follicles and indirectly the number of primordial follicles in the ovaries (Iliodromiti et al., 2015). As such, AMH is now recognized as the best available biomarker of both the functional and true ovarian reserve (Dewailly et al., 2014). Accurate quantitative assessment of the ovarian reserve by AMH (Anderson et al., 2015) has enabled prediction of reproductive lifespan, tailoring of fertility preservation and optimization of assisted conception outcomes (Dewailly et al., 2014; Nyboe Andersen et al., 2017). The recent development of a fully automated Elecsys® AMH immunoassay (Gassner and Jung, 2014) with enhanced sensitivity, specificity and reproducibility, has widened its clinical utility and enabled assessment of women with limited ovarian function.

Women with advanced chronic kidney disease (CKD) often have disturbances in the menstrual cycle and amenorrhoea is common by the time the patient reaches end-stage renal disease (ESRD) (Zingraff et al., 1982). The menstrual cycle typically remains irregular even after the initiation of maintenance dialysis. Consistent with this, pregnancy is extremely uncommon as one progresses from CKD stage 3 to dialysis (Zingraff et al., 1982). Conversely, fertility is frequently restored within a few months after successful kidney transplantation (Levidiotis et al., 2009). To date we are only aware of a single small study ($n$ = 60) assessing AMH in patients with renal failure (Sikora-Grabka et al., 2016). This study utilized a manual AMH ELISA, which was limited by complement interference, irreproducible results and limited sensitivity (Iliodromiti et al., 2015).

The aim of this study was to measure serum AMH concentrations in pre-dialysis, dialysis and kidney transplant women of childbearing age, explore potential factors affecting AMH and compare AMH levels with age-matched healthy controls.

## Materials and methods

### Design and participants

This was a single-centre cohort study of all women aged 18–40 years attending renal services between 1 August 2015 and 31 March 2016 in our catchment area (serving a population of approximately 1.5 million). Potential participants were identified from the electronic patient record used in our centre and by screening clinic lists. A letter was sent to all eligible patients to make them aware of the research, which included an opt-in or opt-out reply slip where they could suggest a way for the research staff to contact them to discuss the study further. If they opted in, they were contacted by a member of the research team to discuss the details of the study and organize a study visit. The protocol of the study was approved by the Research Ethics Committee (REC reference: 15/NS/0040) on 20 May 2015. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

We measured serum AMH levels in three distinct groups of patients: women with CKD stages 3–5, women on haemodialysis (HD) and kidney transplant recipients. We excluded individuals with active or previous cancer (breast, ovarian, lymphoma, pelvic radiotherapy), ovarian surgery, current use of alkylating agent-based protocols, severe active illness and patients unable to provide informed consent.

AMH levels from a multicentre study using the same assay in 600 age-matched healthy women with regular menstrual cycles, not on contraception, were used as the reference group (Anckaert et al., 2016).

### Baseline data

Demographics, aetiology of renal failure, duration of renal replacement therapy (RRT), actual day of the menstrual cycle during the examination, gynaecological history [including menstrual characteristics, number of pregnancies or miscarriages, history of polycystic ovary syndrome (PCOS), family history of premature menopause], and medications potentially (but not definitively) related to AMH concentrations [contraceptives (Bentzen et al., 2012; Deb et al., 2012), prednisolone (Ubaldi et al., 2002) and cyclophosphamide (Clowse et al., 2011)] were recorded.

In addition to AMH, a number of other hormones regulating the ovarian function were measured, including FSH, LH, prolactin, oestradiol and progesterone. Also, serum creatinine, C-reactive protein (CRP) and thyroid hormone blood concentrations were analysed based on literature showing potential associations with AMH (Polyzos et al., 2015; Weghofer et al., 2016; Yarde et al., 2014).

Menstrual cycles were defined as regular when menstrual flow occurred every 21 to 35 days, irregular when menstrual flow occurred less than 21 days or more than 35 days apart, and amenorrhoea was defined as the abnormal absence of menstruation for 90 days or more in accordance with the NICE guideline (NICE, 2014). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate estimated glomerular filtration rate (eGFR) (Levey et al., 2009).

### Study procedures

The blood samples were collected on a random day during the menstrual cycle and then anonymized and centrifuged. In the women on HD, blood samples were obtained before a HD session.

For measurement of AMH, 3 ml serum aliquots for each patient were stored at –80°C. AMH was measured on first thaw of stored samples using an automated method on a clinically validated platform (e411, Roche Diagnostics, Burgess Hill, UK) (Gassner and Jung, 2014). The assay was calibrated and quality controlled using the manufacturer's reagents. Detection limit was 0.01 ng/ml and the coefficient of variation between runs for two levels of control ran at <8%. All AMH samples (including controls) were measured in the same laboratory by the same laboratory-developed test methods in a single run, and all values can therefore be compared uniformly.

All other biochemical parameters were measured using standard assays, in a National Health Service clinical biochemistry department.

### Statistical analysis

We examined differences in demographic characteristics, clinical factors, and biochemical parameters stratified by renal failure group. Continuous variables were expressed with means and SD or medians and interquartile ranges (for non-parametric data), and analysed using parametric and non-parametric tests as appropriate. Categorical vari-



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