International Study on Ovarian Reserve Determination: Practice in ART

1. Introduction and background

Since the beginning of assisted reproductive technology (ART), there has been a need to get a predictive marker of success before ovarian stimulation. The plasma levels of FSH and estradiol (E2), highly variable and dependent on the phase of the menstrual cycle, have led to many inaccurate conclusions. Plasma inhibin B has raised hopes in vain as too dependent on estradiol and FSH and, also, on the size of antral follicles (Grynberg et al., 2010). Anti-mullerian hormone (AMH) plasma level has widely been described as a marker of ovarian reserve (Hazout et al., 2004; Kwee et al, 2008), of ovarian response to stimulation (Hazout et al., 2004; Riggs et al., 2008; Nardo et al., 2009), and of oocyte and embryo quality (Ebner et al., 2006). It also has been advocated as predictive of cycle outcome (Broer et al., 2010; Arce et al., 2013). AMH is a dimeric glycoprotein that belongs to the transforming growth factor β family (Cate et al., 1986).

AMH has supplanted the plasma levels of FSH and Inhibin B, benefiting also from its relative stability during the menstrual cycle, so that the test can theoretically be performed anytime during the cycle (La Marca et al., 2007, 2011). Increasing evidence suggests that AMH is currently the best available test for ovarian reserve testing (Broer et al., 2010, 2014; Arce et al., 2013). Importantly, a recent large prospective (but non-randomized) study suggested that an AMH-based treatment approach for COS may result in reduced treatment burden and reduced risk of hyperstimulation with maintaining pregnancy rates (Nelson et al., 2009). Moreover, inter- and intra-cycle variations are low for AMH, reflecting the non-cyclic (FSH-independent) growth of pre-antral and small antral follicles (Fanchin et al., 2005; La Marca et al., 2006). Therefore, serum AMH measurement appears to be both a reliable and a practical tool for ovarian reserve assessment.

Today, clinicians often offer couples both the plasma level of AMH and the antral follicle count (AFC) in the early follicular phase (Himabindu et al., 2013). The debate remains unresolved about the respective predictive value of these tests, although recently some authors have suggested using AMH alone (Arce et al., 2013; Nelson, 2013), and that it is a "crystal ball for predicting ovarian aging" (Loh and Maheshwari, 2011). Thus, in recent years the determination of AMH levels has become the most used assessment of ovarian reserve. This is also partly because AFC is operator dependent (Broekmans et al, 2010).

Several immunoassays have been commercially available. Precise and accurate immunoassay determinations are a prerequisite for reliable interpretations of AMH results in a clinical setting. However, poor assay reproducibility and sample instability have been described for the widely used GenII AMH ELISA from Beckman Coulter (Rustamov et al., 2012; Zuvela et al., 2013; Clark et al., 2014). Recently, a fully automated AMH immunoassay became available, and showed no evidence of sample instability or variability (Gassner et al., 2014).

2. References

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3. Study objectives

The primary objective of the study is to describe the utilization of AMH in ovarian reserve testing in ART in different countries and centers around the world during the year 2014, i.e. the percentage of cycles in which AMH was determined and the method used to obtain the AMH level.

4. Study type

Descriptive anonymous epidemiological cross sectional study with a questionnaire completed on the Internet by individual ART clinic directors that describes the ART clinic testing practices with respect to IVF in 2014. The questionnaire will contain data summaries by clinic, not individual patient data.

5. Inclusion criteria

All ART centers belonging to countries participating in the ICMART World register on ART through a regional or national register or directly – are eligible to participate.

6. Endpoints

Primary endpoint: Percentage of cases with ovarian reserve determination and distribution of used methods, globally, per country and per region.
Secondary endpoint: potential impact of the type of center and cycle volume on utilization of AMH testing.

7. Investigational plan

7.1. A letter of explanation and information, asking for participation, associated with the protocol summary will be sent to all ICMART participants according to the following method:

- In regions where a regional register exists this letter will be sent to the regional coordinator. This is the case for Europe (ESHRE-EIM), Latin America (RED), North America, Australia and New-Zealand (ANZ), Middle East. According to the register organization, the regional coordinator will send a letter to:
    - National representatives if the regional register is organized by nation: Europe, North-America, ANZ
    - To the clinic directors themselves in other cases: Latin America, Middle-East
- In regions where participation in ICMART is based on a national basis (Asia), the letter will be sent directly to the national representative.
- Finally, where no national/regional registers are functional (most of Africa except for South Africa), the letter will be sent directly to clinic directors.

7.2.In all cases, a letter of explanation, a letter of information and a questionnaire will be sent to each ART clinic participating in the ICMART registry, asking them to complete the questions through a website url which will be provided to them in the email communication.
7.3. The questions will be completed by each ART clinic director on the website developed on the internet to receive the answers to the questions asked.
7.4. Statistical analysis and report will be performed at ICMART.

8. Statistical analysis

Analysis will include 2 steps:

- First, a description of practice and numbers per center and per country, in percentages
- Second, comparisons according to center's status (university / not, private/public) and cycle volume (number of cycles / year)

Methods will include descriptive statistics and chi-square analysis.

9. Report

A report will be written and put on the ICMART website. Scientific publication will be considered as an option.

10. Ethical aspects

Forms will not include any individual patient data.
The center's identification will not be analyzed, but only kept for acknowledgements.
Statistical analysis will not include any patient / center identification, which, in principle means that there is no need for an ethics committee.

11. Financial aspects

The study will be financed through an unrestricted grant from Ferring Pharmaceuticals.