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ARTICLE

Effectiveness of ovarian age as the background risk for aneuploidy screening in an unselected pregnant population

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Maribel Grande obtained her PhD in cellular biology from the University of Barcelona, Spain, in 2005, and then continued her research in developmental biology at CSIC, Spain, until 2009. Over the past few years, her research has focused on first-trimester combined screening, ovarian age, ultrasound anomalies and chromosomal abnormalities.

Abstract The aim of this study was to assess the performance of first-trimester combined screening when replacing the chronological maternal age by Anti-Müllerian hormone (AMH) and antral follicle count (AFC)-derived ovarian ages, as the background risk in trisomy risk estimation. A total of 639 pregnant women who completed first-trimester combined screening together with AMH and AFC determination were included. Trisomy risks were estimated based on three distinct 'maternal ages' as a-priori risk (chronological age, AMH- and AFC-derived ovarian age). The screening performance was assessed using three different approaches: received operator curve; detection rate and false positive rates for a fixed 1/250 threshold; and detection rates for a fixed 3% false positive rate. A non-significant trend was shown for AMH-derived age for both an increased area under the curve (0.986 versus 0.979) and an increased detection rate (from 83% to 100%) for a 1/250 risk threshold. For a 3% false-positive rate, a non-significant trend for increased detection with the use of both AMH- and AFC-derived ovarian ages was observed (from 67% to 83%). These results indicate that, although ovarian derived ages seem to potentially reflect a more precise background risk for fetal trisomies, the improvement in screening performance is only residual.

KEYWORDS: anti-Müllerian hormone (AMH), antral follicle count (AFC), first trimester combined screening, trisomy 21

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Introduction

Maternal age was the traditional method to screen for trisomy 21, and it is still used in many countries to select those women who are liable for cell-free DNA, the most recent and efficient screening method. Over the past 20 years, conventional first-trimester screening has been based on a combination of factors, such as maternal serum and fetal ultrasound markers to modify the inherent maternal age aneuploidy risk. It is now well established that both common (trisomies 21, 18 and 13) and uncommon non-viable autosomal trisomies are clearly related to advancing maternal age (Hassold and Chiu, 1985; Risch et al., 1986), whereas monosomy X and triploidy are not.

Ovarian ageing is expressed by age-dependent decline of the oocyte pool, and can be evaluated by endocrine and ultrasound markers, known as ovarian reserve markers, such as the Anti-Müllerian hormone (AMH) and antral follicle count (AFC) (de Carvalho et al., 2008; Knauff et al, 2009; Broekmans et al., 2009). These ovarian reserve markers are currently used in assisted reproduction as prognostic factors for IVF success. Advanced maternal age can be considered as a surrogate of ovarian ageing, and the increased prevalence of aneuploid pregnancies be attributed to ovarian ageing, particularly to a decline in both quantity of primordial follicles and quality of the oocyte reserve (te Velde et al., 1998). The finding that menopause occurs at an earlier age among women with trisomic pregnancies would support this hypothesis (Kline et al., 2000).

Recently, our group has explored the hypothesis that ovarian-derived age may reflect a more precise background risk for fetal trisomies than the chronological maternal age. Thus, the median AFC-derived ovarian age was found to be 3–5 years above the median chronological age in autosomal trisomies, although no significant differences were observed between AMH-derived ovarian age and chronological age (Grande et al., 2014, 2015). In this study, the chronological maternal age used as the background risk in the first-trimester combined test was replaced by AFC- and AMH-derived ovarian biological ages to estimate trisomy 21 and 18 risks. The idea of using a marker of ovarian age to assess aneuploidy risk has been around for a long time but this is the first study to test it in practice.

Materials and methods

Population

Between April 2012 and December 2013, an unselected pregnant population from the Barcelona-West health district attending for routine first-trimester scan at 11–13 weeks was included in the study. The study population completed the first-trimester combined screening and consented to AMH determination at the time of maternal serum screening and to AFC at the time of the 11–13 weeks scan. Multiple pregnancies and pregnancies achieved by medically assisted reproduction techniques were excluded from the study, as some kind of ovarian stimulation or egg donation was carried out.

Postnatal follow-up was sought in the non-karyotyped low-risk pregnancies. Ethics approval was obtained from the local Research Ethics Committee on 22 March 2011, and written informed consent was obtained from recruited pregnant women. Maternal and clinical data were analysed with the Statistical Package for the Social Sciences (SPSS) version 17 (SPSS Inc., USA).

First trimester maternal serum screening

At 8–12 weeks of gestation, 1 ml of blood was drawn for AMH determination, at the time of maternal blood sampling for free beta-HCG and pregnancy-associated plasma protein A levels assessment. Maternal serum was stored frozen until basal AMH levels (ng/mL) were measured by AMH enzyme immunoassay Gen II (Instrumentation Laboratory and Beckman-Coulter, Vienna, Austria).

First-trimester scan

First-trimester screening was completed at 11–13 weeks with an ultrasound scan carried out by four sonologists, using primarily three ultrasound machines (Acuson Antares, Siemens Medical Solutions, Malvern, PA, USA; Voluson E6 General Electric, GE Healthcare Austria GmbH & Co; and Aloka Prosound α7, Aloka Co. Ltd, Tokyo, Japan). A 25-min slot was assigned for the routine first-trimester scan, which included crown-rump length and nuchal translucency measurement. The AFC was assessed transvaginally according to the technical considerations described by Broekmans et al. (2010). Roughly, round or oval sonolucent structures in the ovaries, not capturing colour flow, were regarded as follicles, but only follicles measuring between 2 and 10 mm in mean diameter were included in the AFC (Grande et al., 2015).

AMH and AFC-derived ovarian ages

Reference ranges for first-trimester AMH and AFC according to maternal age were previously constructed by our group with the use of the Lambda-Mu-Sigma method (Cole and Green, 1992), including only ongoing first-trimester pregnant women with a normal karyotype (Grande et al., 2014, 2015). In each pregnancy, AMH levels and AFC in each pregnancy were translated into a given ovarian age according to the 50th percentile curve for either marker.

Chorionic villi sampling and karyotyping

Chorionic villi sampling was offered to those pregnant women with a risk 1/250 or over for trisomy 21 or for trisomy 18 at the combined test, irrespective of maternal age. Chorionic villi sampling was carried out transcervically under continuous ultrasound guidance (Borrell et al., 1999). Quantitative fluorescent polymerase chain reaction and cytogenetic analysis with both short- and long-term cultures were carried out