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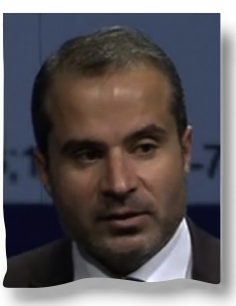
ARTICLE

Is parental consanguinity associated with reduced ovarian reserve?

Tanja Seher [a], Elisabeth Thiering [b], Majdah al Azemi [c], Joachim Heinrich [b], Carsten B Schmidt-Weber [a], Coleen Kivlahan [d,e], Jan Gutermuth [e], Human M Fatemi [f,*]

[a] *ZAUM, Helmholtz Center Munich, Technische Universität München, Biedersteinerstrasse 29, D-80802 Munich, Germany;*
[b] *Institute of Epidemiology I, Helmholtz Center Munich, Ingolstädter Landstr. 1, D-85764 Neuherberg, Germany;*
[c] *Department of Obstetrics and Gynecology, Faculty of Medicine, Kuwait University, Safat, Kuwait;* [d] *Association of American Medical Colleges, 655 K Street, NW, Washington, DC, 20001-2399, USA;* [e] *Department of Dermatology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium;* [f] *IVI–GCC Fertility, Royale Marina, 60202, Abu Dhabi, United Arab Emirates*
* Corresponding author. *E-mail address:* human.fatemi@fatemifertility.com (HM Fatemi).



Professor Fatemi graduated as a MD in 1999 at the Vrije Universiteit Brussel, with magnum cum laude. In 2008 he was recognized as a subspecialist in reproductive medicine and surgery by ESHRE and EBCOG. In 2008 he successfully defended his PhD. He is the author of more than 70 internationally peer-reviewed articles and several book chapters, and has held more than 150 invited spoken presentations. In 2009, at the age of 35, he received the title of Clinical Professor from the University of Brussels. Currently he is working as a director at the Centre for Reproductive Medicine for IVI-GCC in Abu Dhabi.

Abstract This observational study assessed whether women descending from consanguineous unions have reduced ovarian reserve compared with daughters of non-consanguine couples. Two hundred and ninety-one women (≤39 years) were treated in a tertiary care centre in Kuwait. Women underwent a complete anamnesis, including an evaluation of the possible presence of parental consanguinity, transvaginal ultrasound on day 2/3 of the cycle to obtain the antral follicle count (AFC), determination of serum concentrations of FSH, LH, oestradiol and in case of low ovarian reserve (AFC < 9) anti-Müllerian hormone (AMH). The median AFC of non-consanguineous daughters was 11, while daughters from consanguineous parents displayed a significantly lower median AFC (7; $P < 0{\cdot}0001$). FSH was slightly higher in the consanguineous patients, while LH and oestradiol concentrations did not vary between groups. In total, 29.9% of consanguineous patients had an AFC ≥ 9, compared with 63.9% of non-consanguineous patients. Consanguineous patients did not exhibit an age-dependent AFC-decline and displayed reduced AFC and AMH concentrations. The multivariate analysis revealed female consanguinity, as well as surgical history in non-consanguineous women, as strong positive predictors of low ovarian reserve. Parental consanguinity is strongly associated with reduced ovarian reserve. Future studies should evaluate a possible association between parental consanguinity and infertility.

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KEYWORDS: antral follicle count, AMH, consanguinity, female fertility, FSH, ovarian reserve

Introduction

Consanguineous marriage is defined as marriage between second-degree cousins or closer (Bittles, 1994). Twenty per cent of the world population lives in societies where consanguineous marriages are prevalent and approximately 8–10% of children worldwide have consanguineous parents (Alkuraya, 2013; Bittles, 1990; Modell and Darr, 2002).

The prevalence of consanguineous marriages is related to regional and socio-economic factors with relatively low levels in traditional western societies (<1%) and highest levels of >50% in northern and sub-Saharan Africa, the Middle East, and south-east and west Asia, including India, Pakistan and Afghanistan (Bittles, 2001; Bittles and Black, 2010a, 2010b). Consanguineous marriages are reported to confer important social and economic advantages in societies where these unions are highly prevalent. These include strengthening family ties, relative ease of finding a suitable partner, support for the female partner, enhanced relationship with extended family and clarity of inheritance (Bittles et al., 1991). In western societies, much attention has been focused on the increased incidence of autosomal recessive diseases, which are at least ten-fold more prevalent in consanguineous marriages compared with non-consanguineous marriages (Bundey and Alam, 1993).

Despite the known adverse genetic impact of consanguinity, fertility of consanguine couples has been reported to be increased compared with non-consanguine couples, most probably due to younger age at marriage, more stable relationships and higher fecundity as compensation for increased child mortality (Postma et al., 2010). All available studies focus on the fertility of the consanguine couple, but do not evaluate the impact of consanguinity on the fertility of subsequent generations. While the literature is limited, a historic analysis of town and parish registries from isolated Swiss villages suggests that daughters of consanguine parents might have reduced fertility (Postma et al., 2010). In order to investigate the clinical observations, whether parental consanguinity is associated with a reduced ovarian reserve in daughters from consanguineous marriages compared with daughters from non-consanguineous marriages, a series of relevant diagnostic studies were undertaken. Parameters with a potential negative impact on reproductive capacity, including parental kinship, were evaluated.

Materials and methods

Patients, study design and duration

In this observational study, 291 consecutive normally menstruating female patients, aged ≤39 years visiting a tertiary infertility care medical centre in Kuwait between January 2010 and November 2011, were included. Patients underwent complete history (including social/marital history) and physical evaluations, Additionally, diagnostic testing was performed in a single university centre for reproductive health. A transvaginal ultrasound was performed on day 2 to 3 of the menstrual cycle and the antral follicle count (AFC) was determined. The sonographer was blinded to parental kinship. To avoid inter-observer variation, the same investigator performed all scans. On the same day of ultrasound evaluations, all patients underwent a hormonal assessment of FSH, LH and oestradiol. To confirm the reduced ovarian reserve in all patients that showed an AFC of nine or less, the endocrine profile of anti-Müllerian hormone (AMH) concentrations was additionally assessed. For non-English-speaking patients, a trained Arabic/English medical translator assisted the consultant.

The research project was approved by the Institutional Review Board of the "Vrije Universiteit Brussel/Belgium" (OG 016–2011/227, B.U.N.14321112197).

Definition of consanguinity

The status of consanguinity was defined as women whose parents were first-degree cousins (1st degree consanguinity) or second-degree cousins (2nd degree consanguinity). The status of non-consanguinity was defined as daughters from couples who were not related for at least three generations (Bittles, 1994).

Assessment of ovarian reserve

AFC is the most accurate non-invasive measure for ovarian ageing (Rosen et al., 2012). Previous studies have demonstrated that in the age categories included in this study, an AFC of less than nine was a risk factor for infertility (Rosen et al., 2011). Therefore, the patients in this study were classified in the respective groups as normal AFC (≥9) and reduced AFC (<9) categories (Shebl et al., 2011). Ovarian reserve was additionally compared with FSH concentration. To confirm a radiological finding of low AFC, the AMH concentration was determined.

Assessment of AFC

All subjects had a transvaginal scan performed by the same investigator using a Siemens Versa Pro (5–9 MHZ; Siemens, Erlangen/ Germany). A probe program (SIEMENS 7.5L70+) that provided the best image was loaded for each patient and the initially adjusted settings were maintained throughout the examination. A routine ultrasound assessment of the pelvis was first performed to exclude any observable pathology. The ovaries were visualized in the longitudinal plane and the number of antral follicles, measuring 2–10 mm in diameter within each ovary was counted. Follicular size was measured using the internal diameters of the area (La Marca et al., 2013). Two scans were obtained for each ovary. In case of a discrepancy between these two values, a third measurement was done to confirm the final value. The sum of counts in both ovaries produced the AFC.