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The attitudes of Dutch fertility specialists towards the addition of genetic testing in screening of tubal factor infertility

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ABSTRACT

Background: This study aims to identify elements perceived by Dutch fertility specialists as barriers and facilitators for the introduction of genetic testing, and their attitudes towards the use of genetic information. The genetic test would be implemented in routine screening for tubal pathology and identifies SNPs relevant for the immune response causing tubal pathology.
Methods: Experienced reproductive specialists working in Dutch Academic Hospitals were interviewed. Based on the results of four interviews a questionnaire was developed and used to survey medical doctors in six out of eight Dutch Academic hospitals.
Results: 60.4% (n = 91) stated that the addition of genetic markers to the Chlamydia trachomatis antibody test (CAT) in screening for tubal pathology would increase screening accuracy. 68.2% (n = 90) agreed they would require additional training on clinical genetics. Clinical utility (91.2%, n = 91) and cost-effectiveness (95.6%, n = 91) were recognized by the respondents as important factors in gaining support for the new screening strategy.
Conclusion: In summary, respondents showed a positive attitude towards the implementation of a genetic test combined with CAT for tubal factor infertility (TFI) screening. To gain their support the majority of respondents agreed that clinical utility, specifically cost-effectiveness, is an important factor. Comprehensive research about economic implications and utility regarding the introduction of genomic markers should be the next step in the implementation strategy. Furthermore, education and training would need to be developed and offered to fertility care professionals about genetic markers, their interpretation, and implications for clinical decision-making.

Introduction

The importance of genetic information in appropriate clinical management of diseases is increasing [1,2]. Using genetic information in routine clinical practice to provide high quality healthcare is one of the major hallmarks of personalized medicine. Advances in genetics have had clinical implications for the field of gynecology. Genetic testing found its first application in obstetrics/gynecology (OB/GYN) more than three decades ago with prenatal genetic screening for common birth defects during pregnancy [3]. More recently, preimplantation genetic screening has been introduced in the field of assisted reproductive medicine, aiming to improve pregnancy rates in women older than 35 undergoing in vitro fertilization [4]. Additionally, genetic testing for the assessment of a patients risk for hereditary breast and ovarian cancer is routine in obstetric and gynecologic practice [5]. In recent years, genetic testing has been gaining importance in diagnosis of causes of infertility, for example through karyotype analysis [6]. However, to date genetic information has not been used for investigation of tubal pathology in the Netherlands.

One in six couples worldwide are suffering from infertility [7]. In up to 30% of all cases infertility is attributed to tubal factors [8]. As much as 28–62% of tubal pathology can be linked to a previous *Chlamydia* infection [9]. Despite the fact that chlamydial infections are in most cases asymptomatic, and therefore go unnoticed and are not treated with antibiotics, almost half of the women without symptoms clear the infection without any

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treatment within a year [10]. However, other women are prone to persistent infections and consequent complications such as pelvic inflammatory disease, ectopic pregnancy and tubal factor infertility (TFI) [11].

Functional genetic variations, involved in the recognition of bacteria like *Chlamydia* and in the initiation of an adequate immune response, can contribute to higher or lower risk of *Chlamydia* induced TFI [12,13]. Identifying and correlating single nucleotide polymorphisms (SNPs) in pathogen recognizing receptor (PRR) genes with infection outcomes, offers an opportunity for the development of a new TFI screening strategy. Such an assay, which would be performed on human DNA isolated from a blood sample, is under development by an EU consortium. This consortium is called TubaTEST and is funded by the EU Eurostars Programme [14]. Adding genetic biomarkers to the screening for tubal pathology could be more accurate in identifying patients at low or high risk of having tubal pathology [15–17].

Currently, *Chlamydia trachomatis* antibody test (CAT) and hysterosalpingography (HSG) are the most commonly used screening tests for TFI in the Netherlands. They are followed by laparoscopy as the reference diagnostic. Sensitivity and specificity of the most accurate CATs are assessed at approximately 60% and 85–90% respectively [18]. For HSG, these numbers are 53% and 87% [19,20]. Therefore, there is room to increase the accuracy of TFI screening. Combining CAT testing with genetic testing early in the fertility work up could increase the accuracy of such screening and contribute to better triage of women for laparoscopy.

Ultimately though, the ability of genomics to have an impact on clinical practice depends on clinicians' knowledge and attitudes regarding genetic tests. Clinicians make decisions about ordering genetic tests and are responsible for interpreting and explaining the results to patients [21]. Measuring their experiences and attitudes towards the use of genetic tests is increasingly recognized as an important tool for understanding barriers and facilitators for the use of genetic information in diagnosis and treatment of diseases [22–25]. The aim of this study is therefore to identify elements perceived by Dutch gynecologists as barriers and facilitators for the introduction of genetic testing in the routine screening for TFI and to identify respondents' attitudes towards the use of genetic information in the fertility work up.

Methods

The study was performed in two phases, qualitative interviews in the first phase, and quantitative questionnaires in the second. Within the first phase, experienced reproductive specialists working in four Dutch Academic Hospitals were interviewed. The results of these interviews were used to develop a questionnaire. This questionnaire was used in the second phase to survey medical doctors working at OB/GYN departments and providing fertility care in six (75%) Dutch Academic hospitals.

Interviews

Four semi-structured interviews were conducted with four reproductive specialists working in different Dutch academic hospitals in February and March 2013. The purpose of these interviews was twofold: establishing the status quo of fertility work up in the Netherlands, and gain insight into the barriers and facilitators of implementing a genetic test in this work up. The interviews explored: (a) the topic of infertility investigation in general, (b) current guidelines and practices in the screening for TFI, and (c) potential facilitators and barriers for broad implementation of genetic testing in the diagnosis of TFI. Three interviews were conducted face-to-face and one via Skype. Every reproductive specialist was interviewed individually. All the interviews were recorded and later transcribed. The transcripts of interviews were analyzed by coding them for recurring topics. The topics resulting from the interview analysis served as the basis to develop the questionnaire.

Development of the questionnaire

From the interviews, four themes were identified as relevant for the quantitative questionnaire. Each of the themes was further elaborated by defining important elements within them. The themes were: (1) the benefit of genetic testing for routine diagnostics, (2) the characteristics of the test, (3) patients preferences for non-invasive testing, and (4) possible issues around gynecologists' roles and competences related to the introduction of genetic testing in routine fertility work up. For each theme, several relevant barriers and facilitators were identified from the interview data. The elements were then translated into statements to elicit participants' attitudes through the perceived barriers and facilitators. For the purpose of the study, attitudes were understood as defined by Eagly and Chaiken as [26]: "psychological tendency that is expressed by evaluating a particular entity with some degree of favor or disfavor".

In order to assure content validity of the questionnaire the development followed an iterative process. The revisions of the questionnaire were based on multiple rounds of feedback from an experienced gynecologist and an epidemiologist, with expertise in the development and evaluation of health care outcome measures.

The final draft of the questionnaire consisted of 10 questions and 14 statements, divided over three sections. In the first section we asked the respondents six questions about their demographics and level of professional experience. In the second section participants were asked four questions related to immunogenetic research of *C. trachomatis* and its possible implications for the clinical practice. The implications for clinical practice centered on clinical validity and clinical utility. Clinical validity includes analyses of test characteristics, such as the sensitivity and positive predictive value. Clinical utility takes the test a step further and focuses on the impact on care, through analyses such as cost-effectiveness [27,28]. Finally, in the third section we asked the respondents to express their attitudes regarding the possible introduction of a genetic test (see Table 2 in *Results*). Respondents scored each statement by expressing how strongly they agreed or disagreed with it. Each statement had a 5-point Likert scale (agree - disagree), and no opinion as response alternatives.

Conducting the survey

Data was gathered from Dutch Academic hospitals in Amsterdam, Groningen, Maastricht, Rotterdam, and Utrecht in the period May 2014 to July 2015. Visits were organized during department meetings in consultation with the head of the OB/GYN department at each hospital. The participation in the survey was voluntary and the questionnaire was distributed at the department. Only the response of medical doctors were included, regardless of their position, specialization & experience, and was completed on the spot to ensure an adequate response rate.

Data analysis

First, the demographics from section 1 were described followed by the answers to the questions on addressing genetic testing in TFI diagnosis in section 2. For section 3, statements and corresponding answers are shown in Table 2, representing the relative responses on the statements. Furthermore, the items in section 3