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Platinum Priority – Editorial

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A Refined View on the Association Between Y-chromosome Microdeletions and Sperm Concentration

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Infertility is a global health issue that affects up to 15% of couples, with a male factor as a contributing cause in 20–70% of cases [1]. Semen analysis is an essential first step in the evaluation of male infertility, with further evaluation and treatment determined on the basis of the results. However, male infertility is a complex and heterogeneous condition for which the etiology is often unknown. Many of the idiopathic cases of male infertility are thought to be due to unknown genetic defects, as thousands of genes contribute to spermatogenesis [2]. Despite increasing knowledge on genes relevant to spermatogenesis, diagnostic genetic tests in male infertility are largely limited to assessing chromosomal abnormalities, such as Klinefelter's syndrome (47, XXY), and analyses for Y-chromosome microdeletions (YCMs) that remove azoospermia factor (AZF) regions. Partial or complete YCM is considered the most common genetic cause of severe oligozoospermia and azoospermia [3]. According to current European Association of Urology guidelines, testing for YCM is recommended in azoospermic men and severe oligozoospermic men with a sperm concentration of $<5 \times 10^6$/ml [4]. This threshold reflects how most studies on YCM prevalence have made arbitrary divisions in sperm concentration and divided severe oligozoospermia ($<5 \times 10^6$/ml) from oligozoospermia ($5–20 \times 10^6$/ml). Meanwhile, further subdivision of men with sperm concentrations below 5×10^6/ml has not been given much attention.

In this issue of *European Urology*, Kohn and co-workers [5] present a systematic review and meta-analysis of the prevalence of complete YCM in European and North American oligozoospermic men. A total of 37 studies including 12 492 men were identified and 18 cross-sectional studies ($n = 10\ 866$) were included in the meta-analysis (two from North America and 16 from Europe). All YCMs among oligozoospermic men were AZFc microdeletions. The prevalence of YCM was 5% (95% confidence interval [CI] 3.6–6.8%) among men with a sperm concentration of $>0–1 \times 10^6$/ml and 0.8% (95% CI 0.5–1.3%) among men with a sperm concentration of $>1–5 \times 10^6$/ml, with a statistically significant difference between the groups ($p < 0.0001$). Thus, YCM in men with a sperm concentration of $>1 \times 10^6$/ml is rare and, according to this meta-analysis, the prevalence is not different to that for men with higher sperm concentrations. Therefore, the authors propose that the YCM testing limit should be lowered to a sperm concentration of $\leq 1 \times 10^6$/ml.

The study has important strengths. First, it is a well-performed systematic review and meta-analysis that strictly adheres to PRISMA and MOOSE guidelines. Second, the investigators aimed at excluding potential false-positive YCM tests, as only studies using multiplex polymerase chain reaction assessing at least two sequence tag sites per AZF region were included. However, readers should be cautioned on a few points when interpreting the results.

An inherent limitation to the study is the fact that it only includes studies from Europe and North America. This is a problem because significant geographic differences in YCM prevalence have been demonstrated [6]. The authors argue that the inclusion of only European and North American studies is a potential strength as it decreases study heterogeneity, which is true. However, it does limit the generalizability of the results and therefore a YCM testing limit of $\leq 1 \times 10^6$/ml may only be relevant for European and North American reproductive medicine centers. Further-

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more, the study contains no data on YCM prevalence according to ethnicity. This is a general problem in studies investigating YCM prevalence and should receive more attention in future studies, as YCM prevalence might depend not only on geographic but also on ethnicity differences. Another potential limitation is that the authors did not include partial YCM. However, we agree with the authors that the association between partial YCM and semen quality is not well known, and thus the exclusion of partial YCM from the study can be seen as a strength rather than a limitation.

Of note, it is not surprising that only AZFc microdeletions were observed. Complete AZFa and AZFb microdeletions are associated with a severe testicular phenotype demonstrating Sertoli cell–only syndrome and maturation arrest, respectively, and to have sperm in the ejaculate in this situation is highly unlikely. In fact, complete AZFa/b microdeletions are among the only significant negative predictors of surgical sperm retrieval in azoospermic men [7].

The study by Kohn and colleagues [5] is a valuable, clinically applicable contribution to the field of male infertility and on the basis of this large systematic review and meta-analysis it seems relevant for European and North American reproductive medicine centers to lower the YCM testing limit to a sperm concentration of $\leq 1 \times 10^6$/ml. While the study sheds light on YCM prevalence and the association with sperm concentration, it is still remarkable how little is known about the genetic causes of male infertility. Future large-scale studies on new etiological genetic causes of male infertility are needed. In addition, studies investigating YCM should include the ethnicity of the study population.

Conflicts of interest: The authors have nothing to disclose.

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