Asian Journal of Andrology (2014) 16, 929–930

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LETTER TO THE EDITOR

Male Fertility

Human papillomavirus sperm infection: a possible risk factor for male infertility

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Asian Journal of Andrology (2014) **16**, 929–930; doi: 10.4103/1008-682X.137682; published online: 22 August 2014

Dear Editor,

It is well-established that human papillomavirus (HPV)-infection represents one of the most common sexually transmitted infections in both males and females worldwide.[1] Although HPV has been extensively investigated in oncology due to its causal role in cervical and penile carcinogenesis, and also the attachment of HPV to the equatorial region of the sperm head in semen has been clearly observed via optimized *in situ* hybridization technology described by Schillaci *et al.*,[2] relatively little attention has been paid to the issue whether the presence of HPV in semen has significance and consequence for sperm dysfunction and male infertility.[3] In recent times, a well-designed case-control study by Yang *et al.*[4] has comprehensively addressed the clear correlation between HPV sperm infection and male infertility. In this original article, the authors first analyzed the HPV-infection rates in 1138 subjects and demonstrated that the infection rate was 17.4% in the case group (615 infertile males) and 6.7% in the control group (523 fertile males). Later, they conducted the analyses of HPV-positive and HPV-negative semen parameters in the case and control group, respectively. After carefully evaluating the semen volume, pH, concentration, virility, progressive motility (PR) and the normal sperm morphology rate in each pair group, they reached the conclusion that HPV-infection decreased both sperm PR and the normal morphology rate in a statistically significant manner ($P < 0.05$), which may result in impaired male fertility or even infertility. In contrast, the indirect factors such as semen volume, pH and sperm concentration showed no statistically significant differences among each group ($P > 0.05$). In addition, as more than 120 HPV genotypes have been identified, the authors detected and genotyped the 1138 subjects using liquid bead microarray with target-specific probes. Among the 20 HPV genotypes confirmed, they found the most common genotypes in the case group were HPV-45, -16, -52, -18/59, -33 and the most common genotypes in the control group were HPV-68/81, -33, -39 in decreasing order, respectively, further indicting HPV-45, -52, -18, -59 and -16, which are essentially the same as previously identified high-risk types,[2,3] may have close relationships with male infertility.[4] This study is technically sound and provides valuable data to support that HPV-infection is a risk factor for male infertility, particularly by decreasing the sperm PR and normal morphology. Curiously, some previous studies have also focused on elucidating the relationship between HPV-infection with sperm function and male infertility. Whereas, the inconsistent results they obtained made the issue controversial. For instance, in 1997, Lai *et al.*[5] found the incidence of asthenozoospermia among patients infected with either HPV-16 or HPV-18 was significantly higher than in those without HPV-infection (75% *vs* 8%) ($P < 0.01$), and the sperm motility parameters represented by straight-line velocity, curvilinear velocity and mean amplitude of lateral head displacement were significantly affected by the presence of HPV ($P < 0.05$). Paradoxically, Rintala *et al.*[6] claimed that although seminal high-risk HPV DNA was detected in 15.4% of 65 men, and the indirect factor semen pH was subtly lower in HPV DNA positive samples than negative samples (7.4 *vs* 7.5), HPV DNA did not affect semen volume, sperm concentration, motility and viability. Therefore, neither oligo- nor asthenozoospermia was associated with seminal HPV DNA. Another study by Bezold *et al.*[1] presented multiple lines of evidence that semen HPV-infections are frequently seen even in asymptomatic males, and they are often associated with sperm dysfunction, even if the reduction of motile sperm concentration or total motile sperm count was not statistically significant for the HPV-positive group compared with the HPV-negative group ($P > 0.05$). This conclusion was supported by Garolla *et al.*,[7] they addressed that semen volume, pH, total count, normal morphology and viability were not different in the HPV-infected and noninfected samples. However, a significant reduction of mean PR was found in semen samples of infected patients (29.6% ± 14.2%) versus noninfected references (42.4% ± 22.7%) ($P < 0.05$). Later on, two independent studies conducted by the same research group have brought some important clues for us to better understanding the correlation between HPV-infection and male infertility. In 2010, Foresta *et al.*[8] found that semen volume, pH, normal morphology, viability, and even sperm concentration were not different in HPV-infected (HI) and noninfected (HNI) sperm samples. In contrast, a significant reduction of mean sperm motility was found in the 10 semen samples that tested positive for HPV (motility a + b = 53.7% ± 18.2% in HPV-negative group *vs* 37.7% ± 16.8% in HPV-positive group) ($P < 0.05$). In their follow-up study,[9] they divided another cohort of people to distinct groups by strict criterion as Yang *et al.*,[4] namely they distinguished the infertile males with the fertile ones as well as the HI males with the HNI ones, eventually they confirmed a lack of statistically significant difference in semen volume, pH, total count, normal morphology and viability between HI and HNI subjects.[9] Interestingly, in this dual

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Received: 06 April 2014; Revised: 23 May 2014; Accepted: 13 June 2014

Table 1: Sperm parameters observed in the fertile or infertile subjects with HPV-infection or noninfection

Authors	*HPV infected (+) noninfected (–)*	*Fertile (+) infertile (–)*	*Sperm parameters*						
			Volume (ml)	*pH*	*Concentration ($\times10^6$ ml^{-1})*	*Total count ($\times10^6$)*	*PR (%)*	*Normal morphology (%)*	*Virility/ viability (%)*
Yang *et al.*[4]	*n*=142 (+)	*n*=35 (+)	2.31±0.72	7.03±0.32	114.42±61.65	NA	32.25±10.00**	8.51±4.21**	45.83±9.84
		n=107 (–)	2.67±0.79	7.30±0.36	111.31±78.51	NA	20.55±10.44***	4.66±3.08***	37.17±12.53*
	n=996 (–)	*n*=488 (+)	2.72±2.59	7.30±0.35	117.52±84.31	NA	39.22±12.15	13.01±4.50	49.86±12.49
		n=508 (–)	2.65±0.63	7.26±0.31	120.96±85.26	NA	29.11±13.66	8.15±5.05	40.21±13.93
Lai *et al.*[5]	*n*=17 (+)	NA	NA	NA	NA	NA	40.5±18.60*	75.0±7.6	NA
	n=7 (–)						62.7±9.1	79.3±6.1	
Garolla *et al.*[7]	*n*=22 (+)	NA	3.1±0.9	7.6±0.2	29.0±10.3	87.7±36.3	29.6±14.2*	19.0±6.3	81.3±6.3
	n=13 (–)		3.3±1.0	7.5±0.3	30.5±9.8	98.8±46.7	42.4.±22.7	21.1±7.5	83.8±8.3
Foresta *et al.*[8]	*n*=10 (+)	NA	2.9±1.6	7.7±0.3	57.5±30.4	174.3±115.8	37.7±16.8*	31.5±8.0	83.5±7.9
	n=90 (–)		2.4±1.6	7.6±0.2	60.2±31.0	175.8±154.5	53.7±18.2	33.1±11.1	84.6±8.6
Foresta *et al.*[9]	*n*=13 (+)	*n*=2 (+)	2.5±1.6	7.6±0.2	60.5±31.5	175.5±131.6	55.5±17.6	33.5±10.6	81.7±9.4
		n=11 (–)	2.9±1.9	7.7±0.3	30.0±21.5*^	99.4±88.8	33.9±15.9*	32.9±13.9	79.8±8.6
	n=185 (–)	*n*=88 (+)	2.6±1.6	7.7±0.2	58.7±30.8	176.0±139.6	54.2±17.9	33.0±13.5	83.9±8.0
		n=97 (–)	3.0±1.5	7.6±0.3	35.2±23.0*^	102.9±100.9	51.7±16.2	33.1±11.1	84.6±10.7
Rintala *et al.*[6]	*n*=10 (+)	NA	3.7	7.37	96.5#	297.1#	54.2#	NA	NA
	n=55 (–)		4.3	7.51	108.7	412.1	56.5		

*P<0.05; ***P<0.001 versus (infertile) HPV (-) group; **P<0.01 versus fertile HPV (-) group; *^P<0.05 versus both fertile HPV (+) and HPV (-) groups; #P>0.05 versus HPV (–) group. NA: not analyzed; HPV: human papillomavirus; PR: progressive motility. Data are expressed as mean±s.d. or mean value

case-control study, the sperm concentration significantly decreased in the infertile males (HI: 30.0% ± 21.5%, HNI: 35.2% ± 23.0%) compared with the fertile males (HI: 60.5% ± 31.5%, HNI: 58.7% ± 30.8%) (mean value of the total sperm count is also relatively lower, but seems lack of significance), regardless of the presence of HPV-infection. Whereas, the more indicative parameter sperm motility only has a significant reduction between the HI and HNI group in the infertile males (33.9% ± 15.9% *vs* 51.7% ± 16.2%) ($P < 0.05$) but not in the fertile males group (55.5% ± 17.6% *vs* 54.2% ± 17.9%) ($P > 0.05$), indicating it should be of great importance to conduct a thorough analysis via multiparameter grouping, as HI fertile males have distinct sperm functions with HI infertile males, which were definitely proven by the above-mentioned studies.[4,9] To further clarify the controversial issue, we have summarized the representative studies which reported the inconsistent effects of HPV-infection on sperm parameters for indicating male fertility (**Table 1**). From which, we advocate that multiparameter grouping and sufficient subjects like Yang *et al.*[4] should be of considerable importance to draw a convincing conclusion.

In summary, the specific interaction between HPV capsid and receptor localized in the equatorial region of sperm head has been well-documented,[2] and overwhelming evidence suggests a risk factor for HPV-infection in sperm dysfunction (represented by PR) and even male infertility. Screening HPV-infection for infertile males and managing to eliminate the infection may hold great promise in effectively reducing the pregnancy loss rate and early abortion.[3,10]

AUTHOR CONTRIBUTIONS

LZ and ZYH conceived of the study, LZ drafted the manuscript and ZYH revised it. XSZ participated in the design of the study. CZL participated in the design and coordination and critical revision of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 81170698 and No. 81370856), the cultivation project for NSFC at Anhui Medical University (No. 2013KJ14) and Anhui Provincial Natural Science Foundation (No. 1408085QH180). We are also grateful to Dr. Souvik Mendal for helpful discussion in preparing the manuscript.

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How to cite this article: Zhang L, Hao ZY, Zhang XS, Liang CZ. Human papillomavirus sperm infection: a possible risk factor for male infertility. *Asian J Androl* 22 August 2014. doi: 10.4103/1008-682X.137682. [Epub ahead of print]