Sperm morphology from the actual inseminated sample does not predict clinical pregnancy following intrauterine insemination

Jamie Stanhiser, M.D., M.S.C.R.,[a,b] Jennifer E. Mersereau, M.D., M.S.C.I.,[a,b] Daquan Dock, B.S.,[b] Caitlin Boylan, B.S.,[b] Hunter Caprell, B.S.,[b] R. Matthew Coward, M.D.,[b,c] Dara S. Berger, Ph.D.,[b] and Marc Fritz, M.D.[a,b]

[a] Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina; [b] University of North Carolina Fertility, LLC., Raleigh, North Carolina; and [c] Department of Urology, University of North Carolina, Chapel Hill, North Carolina

Objective: To determine the effect of sperm morphology from the specific sample used for intrauterine insemination (IUI) on clinical pregnancy rates (CPR).
Design: Prospective cohort study.
Setting: Academic fertility clinic.
Patient(s): Couples undergoing IUI July 2016–January 2017.
Intervention(s): Morphology slides were prepared from the semen sample produced for IUI.
Main Outcome Measure(s): CPR was measured by detection of cardiac activity. Multiple logistic regression modeling was performed to determine the association of sperm morphology with CPR, controlling for age, antimüllerian hormone level, and post-wash total motile sperm count.
Result(s): Semen analyses, including Kruger strict criteria for morphology from the actual sample inseminated, were reviewed for 155 couples, comprising 234 total treatment cycles. The percent normal morphology significantly differed between the preliminary semen analysis and the IUI sample (−2.0% +3.7% (95% CI −2.55, −1.53). Of the total 234 treatment cycles, 8.6% resulted in clinical pregnancy. When categorized by strict morphology >4%, <4%, and <1%, the CPR was 6.6%, 9.8%, and 10.9%, respectively. In couples with otherwise normal semen parameters (isolated teratospermia), CPR by >4%, <4%, and <1% normal forms was 7.2%, 9.8%, and 11.1%, respectively. There was no significant association between the percent normal morphology and CPR in multivariate analysis.
Conclusion(s): This study evaluating the morphology of the actual inseminated sample did not find differences in CPR following IUI among couples with normal and abnormal sperm morphology, including severe teratospermia. Abnormal sperm morphology should not exclude couples from attempting IUI. (Fertil Steril Rep® 2021;2:16–21. ©2020 by American Society for Reproductive Medicine.)
Key Words: Intrauterine insemination, pregnancy, sperm morphology, teratospermia

Male factor infertility, alone and in combination with female factors, contributes to approximately 50% of infertility diagnoses (1). Semen analysis is used clinically to assess male reproductive function; however, standard semen parameters are not always predictive of pregnancy outcome, particularly morphology, and intersample variation can occur (2). Sperm morphology is an analysis of the percentage of normal forms present in a semen sample, commonly classified using the Kruger strict criteria. The 2010 World Health Organization (WHO) guidelines define the lower limit of normal using Kruger strict criteria to be 4% normal forms; thus, teratospermia is defined to be <4% normal forms (3).

Many studies have examined the impact of sperm morphology on intrauterine insemination (IUI) success in couples, and some have shown that the 4% threshold is clinically significant, while others have found no association (2, 4–10). Recent meta-analyses of the existing literature evaluating the impact of teratospermia, including mild-moderate teratospermia (1%–3% normal

Received August 27, 2020; revised October 29, 2020; accepted November 29, 2020.
All authors have nothing to disclose.
Reprint requests: Jamie Stanhiser, M.D., M.S.C.R., Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of North Carolina, 4001 Old Clinic Building, CB 7570, Chapel Hill, NC 27599 (E-mail: jamie.stanhiser@rpsandiego.com).

Fertil Steril Rep® Vol. 2, No. 1, March 2021 2666-3341

https://doi.org/10.1016/j.xfre.2020.11.007

forms) and severe teratospermia (<1% normal forms), on IUI outcome have concluded that there is no difference in pregnancy success among men with and without teratospermia when accounting for total motile sperm (TMS) count (11, 12). However, all previous studies evaluating the impact of teratospermia have relied on a prior semen analysis for the classification of morphology and not the actual sample inseminated. This may be problematic, as there can be significant variation in semen parameters between samples (13). The classification of normospermia or teratospermia based on the primary semen analysis and not the actual sample inseminated may have confounded the impact of sperm morphology on IUI outcome in the existing literature. Therefore, the aim of this study was to determine the effect of sperm morphology from the specific sample used for IUI on clinical pregnancy rates (CPR). We hypothesized that morphology is not clinically predictive of pregnancy outcome following IUI.

MATERIALS AND METHODS

This was a prospective cohort study performed in an academic fertility clinic under Institutional Review Board approval, which waived written consent. We performed an a priori power analysis assuming an 11% pregnancy rate with IUI in our general infertility population and an effect size of 5% to be clinically meaningful, with alpha 0.05 and power 80%, and determined that 176 couples were required for adequate power. Couples who underwent IUI from July 2016 to January 2017 were enrolled in the study at the time of IUI. Morphology slides were prepared from the semen sample produced for IUI. Semen analyses were performed in accordance with the WHO fifth edition laboratory manual (3). The morphology assessment using Kruger strict criteria was performed by one technician and was batched; the morphology results were not available on the day of the IUI. Exclusion criteria included donor sperm inseminations, no available preliminary semen analysis, baseline semen analysis performed at an outside laboratory, or an undocumented pregnancy outcome. The primary outcome measure for the study was CPR, measured by the detection of cardiac activity via ultrasound. The first analysis consisted of comparing pregnancy outcomes between couples with normal morphology $\geq$4% and otherwise normal semen parameters to those with isolated teratospermia and otherwise normal semen parameters as defined by the WHO fifth edition criteria (morphology <4%, sperm concentration $\geq 15 \times 10^6$/mL, total motility $\geq$40%) (3) and post-wash TMS $\geq 10 \times 10^6$ based on studies affirming this threshold's clinical predictive value and significance for IUI outcomes (4). The latter group was subcategorized for severe teratospermia with <1% normal forms. The second analysis consisted of evaluating CPR in all IUI cycles, with no limitations on other semen parameters, subcategorized by normal morphology, teratospermia, and severe teratospermia.

Semen Analyses

Semen analysis without morphology was performed before each IUI. Andrologists performing the analysis were fully trained and regularly faced internal re-evaluation. The patients were instructed to remain abstinent for 2 to 7 days before the analysis and notify the lab of any missed portion of the sample while collecting; both instances were recorded. Patients whose samples were collected offsite were instructed to keep the sample at room temperature and arrive at the clinic within one hour of the collection. The sample was allowed to liquify at 37°C for 20 minutes before the analysis. The sample was evaluated for sperm concentration, total motility, progressive motility, morphology, and TMS. Volume and viscosity were determined by aspirating the ejaculate with a graduated pipette. Any abnormal debris and viscosity were recorded. Sperm concentration was determined by averaging the number of sperm in two areas on the counting grid of a Makler chamber on a phase-contrast microscope at ×20 magnification. Any counts that had >15% difference were recounted for accuracy. The fraction of progressively motile sperm was determined by counting $\geq$200 sperm in more than five areas of the Makler chamber and classifying them as rapidly progressive, motile nonprogressive, and nonmotile. The presence of round cells was recorded. During this study window, a slide was prepared to assess morphology after the IUI was completed. Slide preparation included smearing 15 μL of semen on a slide before using the Astral Diagnostics Quick III Stain Kit. Slides were dipped 5 to10 times in each solution of the kit then allowed to dry upright. A total of 200 sperm were evaluated per slide according to Kruger strict criteria at ×1,000 magnification on an oil immersion objective (2). Percent normal forms were calculated from the evaluation of 200 sperm. Abnormalities of the head, midpiece, and tail were evaluated, and the percentage of normal sperm was recorded. Quality control was performed by testing the proficiency of technicians semiannually to ensure accurate assessment of semen parameters.

IUI Cycles

Female partners utilized either their natural cycles, ovulation induction, or superovulation using letrozole or clomiphene citrate taken daily on cycle day 3–7, based on the etiology of their infertility. A midcycle transvaginal ultrasound was performed, if indicated, on cycle days 12–14. Mean follicle diameter was calculated, and the number of mature follicles was recorded. Mature follicles were defined as $\geq$14 mm as measured before ovulation. IUI was performed the day after a positive result was detected using an ovulation predictor kit, or approximately 36 hours following a Choriogonadotropin Alfa ovulation trigger injection timed when the lead follicle was $\geq$20 mm in mean diameter as measured by ultrasound.

Our clinic does not have a policy for canceling IUI if the counts are unexpectedly low; however, if the counts are $<2 \times 10^6$ TMS at the time of IUI, the patient is counseled by a physician immediately before the IUI regarding the diminished likelihood of success, and it is the patient's decision to proceed or cancel. We do not have these patients re-collect. We did not make any exclusions for TMS in our study.

Patients were instructed to check a home urine pregnancy test 14 days later. After positive pregnancy tests, a transvaginal ultrasound was performed between 6 and 7 weeks after the last menstrual period to document fetal cardiac activity and pregnancy location. The primary outcome of this study

was a clinical pregnancy defined by the presence of fetal cardiac activity on this early ultrasound.

Statistical Analyses

Univariate analyses were performed to describe the entire cohort. Bivariate analyses were performed with chi-squared test for categorical variables and ANOVA for continuous variables. Pearson's correlation was used to compare pre-wash and post-wash TMS. Multiple logistic regression modeling was performed to determine the association of sperm morphology with CPR, fitted using the generalized estimating equations method. This method was used to account for the correlation of outcomes from multiple cycles from the same patient. An unadjusted model was first made without controlling for any variables. A fully adjusted model was then created by including and controlling for variables found to be statistically different between groups in bivariate analyses or considered clinically meaningful. Variables of female age, antimüllerian hormone (AMH) level, pre-wash and post-wash TMS, and mature follicles in the cycle were modeled continuously, while variables of diagnosis and IUI cycle protocol were modeled categorically. The final adjusted model was made from this fully adjusted model via removing variables in a step-wise fashion. Variables were kept within the model if their removal resulted in ≥10% alteration of the original full model's magnitudes of association or odds ratio, and were excluded from the final model if there was <10% change. This was repeated until the variables removed resulted in the best parsimonious, final model. A paired *t* test was performed to determine if there was a statistically significant difference between percent normal morphology on baseline semen analysis and the actual sample inseminated. $P<.05$ was considered statistically significant. All statistics were performed using Stata 15.

RESULTS

Semen analyses, including morphology scores from the actual sample inseminated, were available for 155 couples comprising 234 total treatment cycles. Of these, 73 couples comprising 91 cycles had ≥4% normal morphology, 107 couples comprising 143 cycles had teratospermia (<4% normal forms), and 45 couples comprising 55 cycles had severe teratospermia (<1% normal forms). Patient characteristics describing the entire cohort are listed in Table 1. The average female age was 34.0 ±4.5 years. Nearly half of couples had unexplained infertility, and over 90% underwent superovulation with clomiphene citrate. The baseline semen analyses of the actual samples inseminated were obtained within 1–6 months. Using Pearson's correlation, pre-wash and post-wash TMS counts were not significantly correlated ($r = -0.193$; $P=.7781$). Mean post-wash TMS was 2.96×10^7, ranging from 1×10^5 to 2.01×10^8. A paired *t* test was performed comparing the percent normal morphology from the baseline semen analysis to the actual sample inseminated; morphology significantly decreased by −2.0% ±3.7% (95% CI −2.55, −1.53, $P<.001$) between samples. In 35.8% of cases, semen analyses with normal morphology (≥4% normal forms) had teratospermia (<4% normal forms) on the actual sample inseminated. In 10.3% of cases, the baseline semen analysis with teratospermia had normal morphology on the sample inseminated. The classification of having normal morphology or teratospermia remained the same between the semen analysis and the inseminated sample in 54.3% of cases.

Normal semen parameters, including ≥4% normal morphology, were observed in 65 couples comprising 83 treatment cycles. Isolated teratospermia (<4% normal forms) and otherwise normal semen parameters were observed in 76 couples comprising 92 treatment cycles. Severe teratospermia (<1% normal forms) and otherwise normal semen parameters were observed in 25 couples comprising 27 treatment cycles. Characteristics by group comparing couples with entirely normal semen parameters to those with isolated teratospermia and isolated severe teratospermia are described in Table 2.

TABLE 1

Characteristics of the total cohort.

Patient & cycle characteristics	N (%) or Mean ± SD
Patient characteristics (N = 155 couples)	
Female age (years)	34.0 ± 4.5
AMH level	3.4 ± 3.8
Diagnosis	
Unexplained	111 (47.4%)
Male factor	54 (23.1%)
Ovulatory dysfunction	29 (12.4%)
Diminished ovarian reserve	25 (10.7%)
Endometriosis	7 (3.0%)
Tubal factor	4 (1.7%)
Uterine factor	4 (1.7%)
Semen analysis parameters	
TMS ($\times 10^6$)	88.9 ± 98.0
Percent normal morphology	4.9% ± 3.7%
Normal (≥4%)	140 (60.0%)
Teratospermia (<4%)	94 (40%)
Mild/Moderate teratospermia (1%–3%)	73 (31.0% of total cohort) (77.7% of teratospermia)
Severe teratospermia (<1%)	21 (9.0% of total cohort) (22.3% of teratospermia)
IUI cycle characteristics (N = 234)	
IUI cycle protocol	
Clomiphene citrate	213 (91.0%)
Letrozole	18 (7.7%)
Natural cycle	3 (1.3%)
Number of mature follicles	2.5 ± 1.0
1	27 (11.7%)
2	93 (40.3%)
3	79 (34.2%)
4	27 (11.7%)
	5 (2.1%)
IUI sample parameters	
Pre-wash TMS ($\times 10^6$)	124.0 ± 169.2
Post-wash TMS ($\times 10^6$)	29.6 ± 36.7
Percent normal morphology	2.8% ± 2.5%
Normal (≥4%)	91 (38.9%)
Teratospermia (<4%)	143 (61.1%)
Mild/Moderate teratospermia (1%–3%)	88 (37.6% of total cohort) (61.5% of Teratospermia)
Severe teratospermia (<1%)	55 (23.5% of total cohort) (38.5% of Teratospermia)
Number of IUI cycles until pregnancy	2.0 ± 1.3

Note: AMH = antimüllerian hormone level; IUI = intrauterine insemination; TMS = total motile sperm.

Stanhiser. IUI morphology doesn't predict pregnancy. Fertil Steril Rep 2020.

TABLE 2

Characteristics by group of normal semen parameters, isolated teratospermia, and isolated severe teratospermia.

Characteristics	Normal semen parameters (65 couples, 83 cycles)	Isolated teratospermia (76 couples, 92 cycles)	Isolated severe teratospermia (25 couples, 27 cycles)	*P* value
Female Age (y, (mean ± SD)	34.0 ± 4.5	34.4 ± 4.5	34.9 ± 5.6	.352
AMH level	3.7 ± 3.3	2.9 ± 2.9	2.7 ± 2.3	.202
Diagnosis				.616
Unexplained	46 (55.4%)	44 (47.8%)	15 (55.6%)	
Male factor	11 (13.3%)	18 (19.6%)	3 (11.1%)	
Ovulatory dysfunction	11 (13.3%)	12 (13.0%)	4 (14.8%)	
Diminished ovarian reserve	8 (9.6%)	12 (13.0%)	3 (11.1%)	
Endometriosis	2 (2.4%)	4 (4.3%)	2 (7.4%)	
Tubal factor	3 (3.6%)	0	0	
Uterine factor	2 (2.4%)	2 (2.2%)	0	
IUI cycle protocol				.008
Clomiphene citrate	70 (84.3%)	87 (94.6%)	25 (92.6%)	
Letrozole	12 (14.5%)	4 (4.3%)	1 (3.7%)	
Natural cycle	1 (1.2%)	1 (1.1%)	1 (3.7%)	
No. of mature follicles				.622
1	12 (14.5%)	10 (10.9%)	2 (7.4%)	
2	32 (38.6%)	41 (44.6%)	15 (55.6%)	
3	28 (33.7%)	29 (31.5%)	7 (25.9%)	
4	9 (10.8%)	12 (13.0%)	3 (11.1%)	
5	2 (2.4%)	0	0	
IUI sample parameters				
Pre-wash TMS ($\times 10^6$)	123.0 ± 136.0	87.9 ± 62.9	43.9 ± 47.3	.045
Post-wash TMS ($\times 10^6$)	42.4 ± 42.3	34.6 ± 40.5	21.3 ± 12.1	.050

Note: AMH = anti-müllerian hormone level; TMS = total motile sperm.

Stanhiser. IUI morphology doesn't predict pregnancy. Fertil Steril Rep 2020.

Compared to couples with ≥4% normal morphology, couples with isolated teratospermia and isolated severe teratospermia underwent fewer letrozole IUI cycles and had significantly lower pre-wash and post-wash TMS.

Of the total 234 treatment cycles included, 8.6% resulted in clinical pregnancy. No miscarriages occurred in our study. Total CPR by ≥4%, <4%, and <1% normal morphology was 6.6%, 9.8%, and 10.9%, respectively (P=.394). In couples with otherwise normal semen parameters, CPR by ≥4%, <4%, and <1% normal morphology was 7.2%, 9.8%, and 11.1%, respectively (P=.547). All CPRs by morphology criteria are listed in Table 3. There was no statistically significant difference in CPR following IUI among couples with ≥4% normal sperm morphology or isolated teratospermia, regardless of the severity of teratospermia. There was no significant association between percent normal sperm analyzed with Kruger strict criteria and CPR in both the unadjusted model and the final model adjusted for female age, AMH level, and post-wash TMS. There was also no association between percent normal morphology on the original semen analysis and CPR.

DISCUSSION

Our study evaluating the morphology of the actual inseminated sample did not find any significant difference in CPR following IUI among couples with normal and abnormal sperm morphology, regardless of severity. The percent normal morphology in the actual sample inseminated was frequently not the same as the baseline semen analysis. Furthermore, the morphology from the original semen analysis was not predictive of clinical pregnancy following IUI. We sought to limit the influence of female age, AMH level, and TMS count as potential confounders, and these were adjusted for in our final model. Additionally, ≥10 × 10^6/mL was analyzed for each group. The findings suggest that sperm morphology is not a clinically significant parameter to predict pregnancy success following IUI in our practice.

Studies have illustrated that with the adaptation of the Kruger strict criteria, sperm morphology classification has shifted over time such that now the average sperm morphology has significantly decreased, with a concomitant increase in the number of men diagnosed with teratospermia (14, 15). These studies' findings suggest that the morphology criteria have become so stringent that its clinical predictive value has been forfeited. Even when the threshold of normal morphology was lowered from 4% to 1% in our study, this did not improve the predictive value for pregnancy following IUI from the original semen analysis or the actual inseminated sample. Our findings support the recent systematic review and meta-analysis of 20 observational studies that were based on the morphology in baseline semen analyses, which concluded that sperm morphology is no longer an adequate predictor for the outcome of IUI, regardless of the severity of teratospermia (12).

Our study has several important strengths. To our knowledge, this is the first study evaluating the impact of sperm morphology from the actual sample inseminated on CPR following IUI. All semen analyses included in this study were performed in the same laboratory with established and proven quality control measures in place. The same technologist assessed all morphology slides. Possible confounding factors, including infertility diagnosis, female age, AMH

TABLE 3

Clinical pregnancy rates by morphology with odds ratios and 95% confidence intervals.

% Normal Morphology	No. of cycles	CPR (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
All treatment cycles				
≥4%	91	6 (6.6%)	0.6 (0.2, 1.7)	0.6 (0.2, 1.6)
<4%	143	14 (9.8%)	1.7 (0.6, 4.6)	1.8 (0.6, 5.1)
<1%	55	6 (10.9%)	1.3 (0.5, 3.3)	2.3 (0.8, 6.6)
Normal semen parameters or isolated teratospermia				
≥4%	83	6 (7.2%)	0.7 (0.3, 1.9)	0.6 (0.2, 1.9)
<4%	92	9 (9.8%)	1.5 (0.6, 3.8)	1.6 (0.5, 4.9)
<1%	27	3 (11.1%)	1.5 (0.5, 4.9)	2.5 (0.8, 7.7)

Note: CPR = clinical pregnancy rates; OR = odds ratio; CI = 95% confidence interval.
[a] Adjusted for female age, antimüllerian hormone level, and post-wash total motile sperm.

Stanhiser. IUI morphology doesn't predict pregnancy. Fertil Steril Rep 2020.

level, post-wash TMS, and the number of mature follicles were adjusted for in our analysis.

Our study has several limitations. First, the sample size may be a significant limitation, as only couples with semen analyses performed in accordance with the WHO fifth edition laboratory manual, including Kruger strict criteria from the actual sample inseminated and a referent baseline semen analysis performed at our andrology laboratory, were included for analysis. Second, ejaculatory abstinence before semen analysis and IUI may have varied. For baseline semen analyses, our common practice is to recommend a period of 2 to 5 days of ejaculatory abstinence before specimen collection. However, the period of ejaculatory abstinence before each IUI may be considerably shorter as couples are actively trying to conceive; this information was not available in the medical record and therefore was unable to be analyzed. Third, couples included in this study underwent natural cycles, ovulation induction, or superovulation with either letrozole or clomiphene citrate, dependent on their overall infertility diagnosis. Although the number of mature follicles was adjusted for to determine the association between sperm morphology and CPR in multiple logistic regression modeling, this may be a limitation. Lastly, regarding the generalizability of our findings, there may be significant interlaboratory variability in semen analyses and particularly in sperm morphology assessment. A 15-year multicenter quality control and assurance study involving 181 laboratories reported a 79.4% variability in sperm morphology assessment across laboratories (16). Future prospective, multicenter studies with larger sample sizes controlling and *standardizing clinical protocol may be valuable to further* describe the potential relationship between sperm morphology and IUI outcome.

The current findings support that Kruger strict criteria do not appear to be clinically significant or a prognostic factor for IUI pregnancy outcomes. It is possible that the current Kruger classification system may have too stringent criteria, and that morphology itself could still be an important parameter under a different classification system.

In conclusion, this study evaluating the morphology of the actual inseminated sample did not find any difference in CPR following IUI among couples with normal and abnormal sperm morphology, regardless of the severity of teratospermia. Abnormal Kruger strict criteria evaluating sperm morphology should not exclude couples from attempting IUI. Future prospective studies with larger sample sizes are needed. Consideration and research to develop a different assessment classification system of sperm morphology that is clinically significant may be warranted.

REFERENCES

1. American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril 2012;98:294–301.
2. Lemmens L, Kos S, Beijer C, Brinkman JW, van der Horst FAL, van den Hoven L, et al. Predictive value of sperm morphology and progressively motile sperm count for pregnancy outcomes in intrauterine insemination. Fertil Steril 2016;105:1462–8.
3. World Health Organization. Laboratory manual for the examination and processing of human semen. 5th ed. Geneva: WHO Press; 2010:271.
4. Shabtaie SA, Gerkowicz SA, Kohn TP, Ramasamy R. Role of abnormal sperm morphology in predicting pregnancy outcomes. Cur Urol Rep 2016;17:67.
5. Mays MK, New EP, Chelmow D, Lucidi RS. Assessing WHO 2010 semen analysis parameters for predicting pregnancy in an infertile population. Fertil Steril 2014;102:e348.
6. Deveneau NE, Sinno O, Krause M, Eastwood D, Sandlow JI, Robb P, et al. Impact of sperm morphology on the likelihood of pregnancy after intrauterine insemination. Fertil Steril 2014;102:1584–90.e2.
7. Erdem M, Erdem A, Mutlu MF, Ozisik S, Yildiz S, Guler I, et al. The impact of sperm morphology on the outcome of intrauterine insemination cycles with gonadotropins in unexplained and male subfertility. Eur J Obstet Gynecol Reprod Biol 2016;197:120–4.
8. Gatimel N, Moreau J, Parinaud J, Léandri RD. Sperm morphology: assessment, pathophysiology, clinical relevance, and state of the art in 2017. Andrology 2017;5:845–62.
9. Lockwood GM, Deveneau NE, Shridharani AN, Strawn EY, Sandlow JI. Isolated abnormal strict morphology is not a contraindication for intrauterine insemination. Andrology 2015;3:1088–93.
10. Sun Y, Li B, Fan LQ, Zhu WB, Chen XJ, Feng JH, et al. Does sperm morphology affect the outcome of intrauterine insemination in patients with normal sperm concentration and motility? Andrologia 2012;44:299–304.
11. Ombelet W, Dhont N, Thijssen A, Bosmans E, Kruger T. Semen quality and prediction of IUI success in male subfertility: a systematic review. Reprod Biomed Online 2014;28:300–9.
12. Kohn TP, Kohn JR, Ramasamy R. Effect of sperm morphology on pregnancy success via intrauterine insemination: a systematic review and meta-analysis. J Urol 2018;199:812–22.
13. Poland ML, Moghissi KS, Giblin PT, Ager JW, Olson JM. Variation of semen measures within normal men. Fertil Steril 1985;44:396–400.

14. Morbeck DE, Leonard PH, Weaver AL, Shimek KM, Bouwsma EV, Coddington CC. Sperm morphology: classification drift over time and clinical implications. Fertil Steril 2011;96:1350–4.
15. Menkveld R. Clinical significance of the low normal sperm morphology value as proposed in the fifth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen. Asian J Androl 2010;12:47–58.
16. Punjabi U, Wyns C, Mahmoud A, Vernelen K, China B, Verheyen G. Fifteen years of Belgian experience with external quality assessment of semen analysis. Andrology 2016;4:1084–93.