Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2021, 11, 88-101
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

The Presence of Antisperm Antibodies in Semen of Subfertile Men

—Positive ASA in Subfertile Men

Kim Kamphorst*, Joyce Faber, Paul Jan Quirien van der Linden

Deventer Ziekenhuis, Department of Gynaecology, Obstetrics and Reproductive Medicine, Deventer, The Netherlands
Email: *k.kamphorst@dz.nl

How to cite this paper: Kamphorst, K., Faber, J. and van der Linden, P.J.Q. (2021) The Presence of Antisperm Antibodies in Semen of Subfertile Men—Positive ASA in Subfertile Men. *Open Journal of Obstetrics and Gynecology*, **11**, 88-101.
https://doi.org/10.4236/ojog.2021.112011

Received: January 11, 2021
Accepted: February 22, 2021
Published: February 25, 2021

Abstract

Background: In more than 50% of male subfertility, the aetiology remains unknown. Antisperm antibodies (ASA) might be involved, however the exact role of ASA in unexplained male subfertility is not clear, yet. *Objective*: The aim of this study was to examine 1) the prevalence of ASA in subfertile men, 2) the possible causes of the presence of ASA, and 3) the influence of ASA on sperm parameters and fertilization including assisted reproductive technologies (ART) and pregnancy outcomes. *Study Design*, *Size*, *Duration:* In this retrospective single center study, all men with semen analyses between January 2003 and December 2017 were included as well as all subfertile couples getting treatment if at least one sperm analysis showed a spermMar test ≥50%. *Methods*: Collected parameters were: intoxications, medication and professions that could have an adverse effect on fertility, sperm parameters, the type and amount of ART, mode of conception, pregnancy rates and outcomes. *Results*: 3098 semen analyses were performed. In total, 233 ASA positive men were observed, including 175 subfertile couples with an ASA positive man in the additional analyses. The prevalence of ASA in the subfertile population was 8.2%. The presence of ASA was significantly associated with the presence of oligoasthenoteratozoospermia (OAT), asthenoteratozoospermia and asthenozoospermia ($p = 0.008$, $p = 0.004$, and $p = 0.02$ respectively). However, 50% of the couples with an ASA positive man became pregnant without ART. *Conclusions*: The presence of ASA did not seem to have a negative effect on spontaneously pregnancy rates or pregnancy rates after ART. Therefore, it might be justified to advice 6 - 12 months expectant management, before starting ART in ASA positive men.

Keywords

Retrospective, Antisperm Antibodies, Infertility, IgG, IgA

1. Introduction

Male subfertility affects up to 12% of men, in which more than 50% of this male subfertility cannot be explained [1]. One of the proposed causes for unexplained male subfertility is the presence of antisperm antibodies (ASA). ASA are immunoglobulins directed against antigens of the sperm surface [2]. In 1954, the influence of ASA on subfertility has been reported for the first time yet, by Wilson and Rumke. Afterwards, many studies were performed to examine the effect of ASA on subfertility [3] [4].

Over the years, two different isotypes of ASA have been identified; Immunoglobulin A (IgA) and Immunoglobulin G (IgG). According to the current guidelines (2010) of the World Health Organisation (WHO), the SpermMAR test and the direct immunobead test are conventional techniques to identify the presence of ASA [5]. A SpermMAR test of ≥50% motile spermatozoa with adherent particles is considered as positive [5]. Since former WHO guidelines recommended various techniques to identify the presence of ASA and advised a cut-off value of ≥10%, it is challenging to estimate and to compare the exact prevalence of ASA. In literature, the prevalence of ASA in all subfertile men varies between 1% - 13%, depending on the screening method and the cut-off value used, compared to 1% - 2% infertile men [6] [7] [8]. Nevertheless, the exact incidence for the presence of ASA remains largely unknown.

There have some possible causes for the presence of ASA been described. It is suggested that sperm antigens are exposed to the immune system by interruption of the blood-testis barrier [9]. This interruption could occur due to an infection of the testis (epididymitis or orchitis), trauma of the vas deferens or mechanical injury of the testis such as a vasectomy or a vaso-vasostomy, leading to an immune response including the production of ASA. Subsequently, this can result in damage of the vas deferens leading to an adverse effect on the sperm quality [10] [11] [12]. Despite the associations observed so far, the cause for positive ASA is not exactly known in subfertile men.

The presence of ASA may affect the fertilization process and hence the opportunity on pregnancy on several levels. ASA can reduce sperm forward progressive motility and may affect sperm penetration through cervical mucus [13] [14]. In addition, ASA may disrupt sperm-oocyte recognition and fusion by preventing sperm from undergoing maturation and acrosome reactions. Possibly, ASA antibodies may limit the sperm-oocyte recognition and fusion and negatively affect fertilization through suboptimal function of the sperm [15] [16]. Accordingly, if ASA is identified during the fertility work-up in the absence of pregnancy after one year or more of regular unprotected sexual intercourse in the Netherlands, intrauterine insemination (IUI) can be advised [17]. Assisted reproductive technologies (ART) however, are expensive and could have a major emotional impact. Furthermore, studies examining the influence of ASA on fertilization show conflicting results and have generally been published before 2010 with the use of former WHO guidelines. Therefore, it is relevant to examine

whether the presence of ASA should be taken into account in the decision-making process regarding starting ART.

In summary, the incidence of ASA in subfertile men, the causes for ASA and the effect of ASA on men's fertility are still unclear. Therefore, the aim of this study was to examine 1) the prevalence of ASA in subfertile men, 2) the possible cause for the presence of ASA, and 3) the influence of ASA on sperm parameters and fertilization, including different ART and pregnancy outcomes.

2. Method

2.1. Study Design and Setting

In this retrospective single center study, all men with semen analyses performed at the laboratory the Deventer Hospital between January 2003 and December 2017 were included. The Deventer Hospital is a teaching hospital in the Netherlands. Around 280 semen analyses are performed each year. Semen analysis is performed according to the current WHO guidelines, in which the SpermMAR test (FertiPro, Beernem, Belgium) is routinely performed [5]. The gynaecologist generally performed a semen analysis as part of the fertility work-up, including an ovulation assessment, a post coital test and a Chlamydia-antibody test (CAT), as well. Depending on the results of the fertility work-up and the calculated prognosis on a spontaneous pregnancy in one year, based on Hunault if applicable, couples were advised to expected management for a certain period or to start with ART [18].

2.2. Sub population

To examine the influence of ASA on subfertility, a sub population was identified. In this sub population all subfertile couples who were under treatment of a gynaecologist between January 2003 and December 2017 were included if at least one sperm analysis showed the presence of an IgG and/or IgA spermMar test percentage of ≥50%. Couples were excluded when the woman had an anovulatory cycle that could not be corrected with ovulation induction, or in case of bilateral occlusion of the fallopian tubes.

2.3. Objectives

The primary parameters of the study were the presence of ASA in all semen analysis during the study period and the incidence of ASA in the subfertile population.

The other parameters that were investigated were the incidence of men who had a plausible explanation for the presence of ASA, such as operations and their medical history. Furthermore, the influence of ASA on sperm parameters and fertilization, including the spontaneous pregnancy rate were measured. In addition, the type and number of ART such as IUI, in vitro fertilization (IVF) and/or Intracytoplasmic Sperm Injection (ICSI), and pregnancy outcomes were measured in the subfertile population with a positive ASA male.

2.4. Data Collection and Parameters

The following parameters were anonymously collected from the electronic patient data system: age (at first visit at the gynaecologist), race, BMI, duration of subfertility (time between the pregnancy wish and the start of ART), duration of the pregnancy wish (time between the pregnancy wish until the onset of a pregnancy), and a history of conditions that could negatively affect fertility. The following environmental factors were noted: intoxications, medication that could have an adverse effect on fertility such as testosterone [19]. Furthermore, professions that are known to influence fertility were noted such as CO_2 welding or irregular shifts [20] [21]. Variables were excluded in case of more than 10% missing values, to avoid bias [22].

In men, sperm parameters (concentration, motility, morphology and the percentage of IgG and IgA) of all semen analyses during the study period (2003-2017) were retrieved from the data system of the laboratory. If more than one sperm analysis of a man was present, the sperm analysis with the highest percentage of IgG and IgA was used for analysis.

In women, the type and number of ART, the mode of conception, the number of pregnancies and the pregnancy outcome after ART were examined. A pregnancy was defined as a clinical pregnancy demonstrated with a pregnancy test and/or ultrasound.

Furthermore, to examine the influence of ASA on fertility, pregnancy rates after IUI between 2011 and 2017 were examined. Pregnancy rates after IVF/ICSI in the Deventer hospital between 2003 until 2016 were collected as well, since the treatments that have started in 2017 have not all been completed during the study period, yet.

2.5. Statistical Analysis

Data were analyzed using SPSS Statistics for windows, version 24.0 (Armonk, NY) [23]. Descriptive statistics were presented in means and standard deviations for continuous and normally distributed variables; median and interquartile ranges for continuous non-normally distributed variables and proportions and absolute numbers for categorical variables. A Chi squared test/Fisher's exact test as appropriate was performed on dichotomous variables. A p-value of <0.05 was considered significant.

2.6. Ethical Approval

The local medical ethics committee of the hospital obtained ethical approval (n-WMO), reference number ME-17-69, in accordance with the Declaration of Helsinki.

3. Results

3.1. Prevalence of ASA

During the study period 4283 sperm analyses were performed, of which 28%

were repeated semen analyses. After exclusion of these repeated analyses, 3098 semen analyses remained (see Figure 1). In the 3098 semen analyses, 233 analyses with positive ASA were described, resulting in an incidence of 7.5%. From the 233 ASA positive men, 182 got a fertility work-up and from the 3098 men who had semen analyses, 2229 visited the gynaecologist for a fertility work-up. Resulting in an incidence of ASA of 8.2% in the subfertile population, defined as a pregnancy failure after one year or more of regular unprotected sexual intercourse.

For the sub analyses of ASA in the subfertile population (n = 182), the couples with female subfertility were excluded (n = 7), resulting in the inclusion of 175 couples. For the other analyses, all 233 ASA positive male were included.

3.2. Patient Characteristics

The mean male age was 34.8 (± 6.7) years at the start of the fertility work-up (Table 1). Ten of the 175 men were known to have a profession associated with reduced sperm quality, with CO_2 welder occurring most frequently. Eight men were known to use medication (e.g. prednisone, testosterone, paroxetine and cladribrin) that could have a negative influence on the quality or quantity of the sperm. However, none of these men had an oligoasthenoteratozoospermia (OAT) (sperm concentration of $<15 \times 10^6$/ml, progressive motility of <32% and less than 4% of the spermatozoa with normal morphology) or oligospermia. Six men had an existing condition or condition in the past that could have a negative effect on fertility, such as a malignancy requiring chemotherapy or a testosterone deficiency.

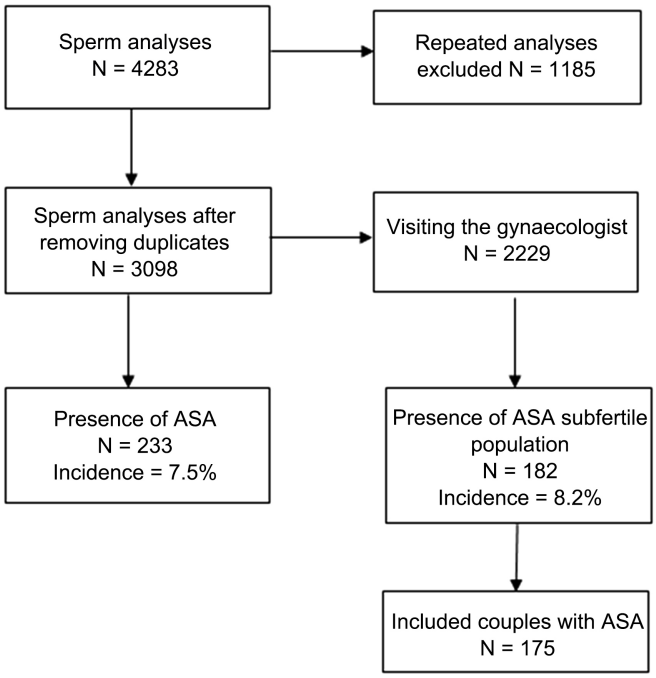

Figure 1. Flow diagram of included sperm analyses. Couples (n = 7) were excluded when the woman had an anovulatory cycle that could not be corrected with ovulation induction, or in case of bilateral occlusion of the fallopian tubes.

Table 1. Patient characteristics of the 175 subfertile couples with ASA positive men.

	Male characteristics
Age mean (± SD)	34.8 (7)
Race N (%)	
Caucasian	171 (98%)
Smoking N (%)	
Yes	61 (35%)
No	84 (48%)
Unknown	30 (17%)
Alcohol N (%)	
Yes	99 (57%)
No	44 (25%)
Unknown	32 (18%)
Drugs N (%)	
Yes	5 (3%)
No	132 (75%)
Unknown	38 (22%)
Professions with negative effects on fertility[1] N (%)	10 (6%)
CO_2-welder	5 (3%)
With solvents	4 (2%)
With oil	1 (1%)
No	119 (68%)
Unknown	46 (26%)
Medication possible affecting fertility[2] N (%)	8 (5%)
Sexual dysfunction	8 (5%)
Decreased quality/quanitity of the sperm	6 (3%)
No	165 (94%)
(Former) disorders affecting fertility N (%)	6 (3%)
Malignancy	2 (1%)
Chemotherapy	2 (1%)
Retractlie testicle	1 (1%)
Testosterone deprivation	1 (1%)
Suppletion	2 (1%)
Spermatocele	1 (1%)
No	168 (96%)

[1]A possible negative effect on sperm parameters or fertility as described in literature; [2]Sexual dysfunction or decreased libido were not present and the decreased quality of the sperm did not cause the presence of an OAT.

3.3. Causes of ASA

To identify causes of ASA, all 233 ASA positive men were analyzed. In 79 of the 233 ASA positive men a plausible cause of ASA was reported, while in 27 documentation was missing. The most common causes of ASA were a vasectomy, a vasovasostomy (n = 57) and an inguinal hernia (n = 10). Other reported causes were an operative corrected cryptorchism (n = 8), an epididymitis (n = 6), a trauma of the genital area (n = 3), an operative corrected varicocele (n = 1) and a testical carcinoma (n = 1).

3.4. Sperm Parameters

No association was found between professions associated with reduced sperm parameters and the occurrence of an OAT. However, ASA positive men had significantly more often an abnormal sperm analysis defined as the presence of an OAT, oligoasthenozoospermia (OA), oligoteratozoospermia (OT), asthenoteratozoospermia (AT), oligozoospermia (O), asthenozoospermia (A) or teratozoospermia (T) compared to ASA negative men (64% vs 56%, p = 0.02). From the 233 men with positive ASA, only 85 men (36%) had no other abnormal sperm parameters. The ASA positive men with aberrant sperm analyses had significantly more frequent an OAT compared to ASA negative males (12% vs 8%, p = 0.008). In addition, significantly more ASA positive men had an asthenoteratozoospermia and an asthenozoospermia compared to ASA negative men (p = 0.004, and p = 0.02, respectively), see Table 2.

Of the 233 ASA positive men, 226 men (97%) had positive IgG ASA, and 56 (24%) positive IgA ASA. In total, 163 men were observed with only positive IgG ASA (70%), and seven men with only positive IgA (4%). Positive IgG ASA were observed in all men after a vasectomy and vaso-vasostomy. Positive IgA was only diagnosed in 27 men with a vasectomy and vaso-vasostomy.

Table 2. Overview of sperm parameters of the 3098 performed semen analyses between 2003-2017.

	ASA positive men N%	*ASA negative men* N%	*Significance*
Abnormal sperm parameters	148 (64%)	1602 (56%)	***p* = 0.02**
OAT	29 (12%)	216 (8%)	***p* = 0.008**
OA	12 (5%)	84 (3%)	*p* = 0.06
OT	12 (5%)	214 (8%)	*p* = 0.19
AT	27 (12%)	189 (7%)	***p* = 0.004**
O	7 (3%)	121 (4%)	*p* = 0.37
A	17 (7%)	118 (4%)	***p* = 0.02**
T	44 (19%)	660 (23%)	*p* = 0.15
Total	233	2865	

OAT: oligoasthenoteratozoospermia, OA: oligoasthenozoospermia, OT: oligoteratozoospermia, AT: asthenoteratozoospermia, O: oligozoospermia, A: asthenozoospermia, T: teratozoospermia.

3.5. ART in Subfertile Couples with an ASA Positive Man

The median duration of subfertility at the first visit to the gynaecologist for a fertility work-up of the 175 couples was 16 months (IQR 12 - 24). After one year of expectant management, 104 of the 175 couples received ART consisting of IUI, IVF and/or ICSI.

Ninety of the 104 couples started an IUI treatment. From these couples, 37 continued with IVF after IUI treatment was not successful after 4 - 6 cycles and 15 couples switched to ICSI thereafter. Fourteen couples switched to ICSI after IUI because of a VCM (volume, count and motility) of less than 1 million. This VCM was determined during the semen analyses for IUI treatment.

Four of the 104 couples were primarily advised to start with IVF because of a VCM around 1 million, followed by ICSI in two of the four couples because of the absence of a pregnancy and a VCM of less than 1 million. Ten couples were directly advised ICSI because of a VCM of less than 1 million.

3.6. Pregnancies

In total, 69 of the 175 couples (39%) get pregnant spontaneously in the year of expectant management or during the ART treatment, despite the presence of ASA (Table 3). Furthermore, in 18 couples (10%) a spontaneous pregnancy occurred, but ART treatment was needed for another pregnancy. Of the 175 couples, 27 (15%) couples became pregnant after IUI treatment, 21 (12%) after IVF treatment, 30 (17%) after ICSI treatment and 34 (19%) women did not became pregnant. The median duration between a pregnancy wish and onset of the first pregnancy was 26 months (IQR 17 - 37) ranging from 20 months in the group of spontaneous conception (IQR 14 - 31) to 36 months in the group of ICSI (IQR 25.5 - 50.5).

Table 3. Overview of assisted reproductive technologies (IUI, IVF, and ICSI), way of conception and pregnancy rates in the 175 couples with ASA positive men.

	Spontaneous pregnancy	IUI	IVF	ICSI
Number of treatments	-	397	75	94
Number of couples	85	90	41	41
Number of pregnant couples	87	27	21	30
Number of pregnancies[1] N%	131 (53%)	40 (16%)	37 (15%)	40 (16%)
Pregnancy rate per treatment	NA	10%	36% incl. cryo 49%	32% incl. cryo 45%
Pregnancy rate per couple	50%	30%	46% incl. cryo 51%	63% incl. cryo 73%
Time from pregnant wish-onset first pregnancy (in months)	20 (IQR 14 - 31)	27 (IQR 22 - 32)	33 (IQR 29 - 53)	36 (IQR 26 - 51)

[1]In some couples more than one pregnancy occurred.

Pregnancy rates after ART

IUI was performed in 90 of the 175 couples. A total of 40 pregnancies occurred in 27 couples, since in some couples more than one pregnancy occurred. The pregnancy rate per IUI cycle per couple was 10%, and the total rate per couple 30%.

Forty-one of the 175 couples had one or more IVF treatments, leading to 37 pregnancies in 21 couples. The pregnancy rate per IVF cycle per couple was 36% in couples with ASA positive men, while the average pregnancy rate per cycle of all performed IVF cycles in our hospital was 30% without including cryo transfers. The pregnancy rate after IVF per couple was 46% and increased to 51% when including cryo transfers.

Forty-one of the 175 couples had one or more IVF/ICSI treatments. A total of 40 pregnancies were observed in 30 couples. The pregnancy rate per ICSI cycle was 32% in couples with ASA positive men, compared to an average pregnancy rate of 28% per cycle of all ICSI cycles performed without including cryo transfers. The total pregnancy rate after ICSI per couple was 63% and increased to 73%when including cryo transfers.

3.7. Pregnancy Outcome

Of the 248 pregnancies that occurred, 183 ended in a live birth (74%), and 60 ended in a miscarriage <16 weeks (24%). Five pregnancies ended in a non-live birth after 16 weeks (2%). Except for two children that were born at 36 weeks of gestation (1%), all children were born at term.

4. Discussion

The aim of this study was to examine the influence of ASA on male subfertility. The observed incidence of ASA in our subfertile population was 8.2%. In only one third of all ASA positive men, a plausible explanation for the presence of ASA could be observed.

Subfertile men with ASA had significantly more often an abnormal sperm analysis compared to men without ASA. However, the presence of ASA did not appear to have an adverse effect on fertility rates after ART. Moreover, about half of the subfertile couples with ASA positive men became spontaneously pregnant during the course of their work-up.

While it is difficult to compare the observed prevalence of 8.2% in the ASA positive man with other studies [24] [25], the current WHO guidelines are used and the incidence is examined over a period of 14 years in a relative large study population. For that reason, we think that this prevalence can be considered representative for subfertile men in a teaching hospital.

Contrary to the prevalence, the causes of the presence of ASA were comparable with literature. The most common cause for positive ASA was a vaso-vasostomy after a vasectomy, as also was described by Chamley *et al.* [26]. Unfortunately, the cause for positive ASA remained largely unknown in the majority of the men in this study. As described, ASA has been shown to occur more frequently in

disorders that could disrupt the blood testis barrier, however, it could be that not all disorders disturbing the blood testis barrier are noted [9]. Some men may for example have experienced mild orchitis or epididymitis that is not reported. Therefore, it is probably not possible to find an explanation for the presence of ASA in all men with positive ASA.

Possibly, it is not that relevant to find an explanation for the presence of ASA, since almost 50% of the couples in this study got spontaneously pregnant during the fertility work-up or during the 6 - 12 months of expectant management. Previously, varying results were found when examining the influence of ASA on spontaneous pregnancy rates [7] [27]. It is debatable whether the presence of ASA without an OAT should be taken into account in the advice to start ART, also for men after a vasectomy and vasovasostomy, considering the relatively high chance of spontaneous conception. Therefore, expectant management for a period of 6 - 12 months in men with positive ASA without an OAT could be preferable compared to starting ART.

If ART is started, the presence of ASA did not appear to have any adverse effect on the pregnancy rates. A pregnancy rate of 10% after IUI treatment for couples with an ASA positive male was comparable with the general Dutch pregnancy rate of 9% after IUI [28]. The comparable pregnancy rate might be explained by the fact that in our hospital sperm is collected in medium, which may result in less agglutination of the sperm with ASA and therefore in a better quality [29]. Accordingly, the quality of the sperm in both ASA positive and ASA negative male seems comparable. To our knowledge, no randomized study has been performed that examined the additional value of IUI in couples with an ASA positive male. Scarce literature on open label studies showed conflicting results with regard to the influence of ASA on pregnancy rates after IUI [30] [31]. In the present study, a lower percentage pregnancy is observed in couples in which the man had an OAT, both in ASA positive, as well as in ASA negative men. This might suggest that pregnancy rates after IUI are not dependent on ASA but on the presence of an OAT.

More than a third of the couples continued with IVF and/or ICSI after IUI, in which the chances on pregnancy were still relatively good. The clinical pregnancy rates in the present study after IVF and ICSI (36.0% and 31.9%, respectively) were in the ASA positive group slightly higher compared to the total group (29.9% and 27.9%, respectively), and appeared to be also higher than the Dutch pregnancy rates after IVF and ICSI (26.1% and 29.4%, respectively) [32]. In line with these findings, meta-analyses by Zini *et al.* showed that the presence of positive ASA was not associated with reduced fertility after IVF and ICSI [25].

Strengths of this study were that the data were collected over a long period of 14 years. As a result, more than 4000 sperm analyses could be obtained and a relatively large group of couples with ASA men could be analyzed, leading to an incidence of 8.2%, which is representative for the subfertile population of secondary teaching hospitals. In addition, many parameters were included in this study that might have an influence on subfertility. The ART were carried out

according to guidelines of the Dutch association of obstetrics and gynaecology (NVOG). All parameters that might be relevant to demonstrate an association between ASA and fertility were collected. As a result, the present study provided a detailed overview of the relevant characteristics of the couples with ASA positive men.

Some limitations need to be considered. This study was a single center retrospective study. Therefore, it was inevitable that some values were missing. Moreover, we still have no explanation for the presence of ASA in the majority of man. Furthermore, no distinction was made between men with and without an OAT who received IVF or ICSI, as well as between IgG ASA and IgA ASA because of the relatively small size of these groups. In this group of men, any negative influence of an OAT could therefore not be excluded, nor was it possible to distinguish between the different types of ASA on fertility. Finally, because this is an observational study, we can only examine associations instead of causation.

5. Conclusion

The incidence of ASA in the subfertile population was 8.2%. Almost 50% of the couples with an ASA positive man became spontaneously pregnant. Therefore, an expectant management policy for 6 - 12 months might be justified in couples with an ASA positive man, but only when OAT or other abnormal semen factors are absent. Although the presence of ASA has been associated with poor sperm parameters, it seems not to influence the pregnancy rates after assisted reproductive technologies.

Author's Contribution

Conception or design of the work: K.Kamphorst, J. Faber, P.J.Q. van der Linden.
Data collection: K.Kamphorst.
Data analysis and interpretation: K.Kamphorst, P.J.Q. van der Linden.
Drafting the article: K.Kamphorst, P.J.Q. van der Linden.
Critical revision of the article: K.Kamphorst, J. Faber, P.J.Q. van der Linden.
Final approval of the version to be published: K.Kamphorst, J. Faber, P.J.Q. van der Linden.

Statement of Ethics

The local medical ethics committee of the hospital obtained ethical approval (n-WMO) by the medical ethical review committee (METC) of the Isala Clinics in Zwolle, The Netherlands. Reference number ME-17-69, in accordance with the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Ghuman, N. and Ramalingam, M. (2018) Male Infertility. *Obstetrics, Gynaecology & Reproductive Medicine*, **28**, 7-14. https://doi.org/10.1016/j.ogrm.2017.10.007

[2] Naz, R.K. and Menge, A.C. (1994) Antisperm Antibodies: Origin, Regulation, and Sperm Reactivity in Human Infertility. *Fertility and Sterility*, **61**, 1001-1013. https://doi.org/10.1016/S0015-0282(16)56747-8

[3] Rumke, P., Van Amstel, N., Messer, E. and Bezemer, P. (1974) Prognosis of Fertility of Men with Sperm Agglutinins in the Serum. *Fertility and Sterility*, **25**, 393. https://doi.org/10.1016/S0015-0282(16)40388-2

[4] Wilson, L. (1954) Sperm Agglutinins in Human Semen and Blood. *Proceedings of the Society for Experimental Biology and Medicine*, **85**, 652-625. https://doi.org/10.3181/00379727-85-20982

[5] WHO Cooper TG (2010) WHO Laboratory Manual for the Examination and Processing of Human Semen.

[6] Adeghe, J.H.A. (1993) Male Subfertility Due to Sperm Antibodies: A Clinical Overview. *Obstetrical & Gynecological Survey*, **48**, 1-8. https://doi.org/10.1097/00006254-199301000-00001

[7] Ayvaliotis, B., Bronson, R., Rosenfeld, D. and Cooper, G. (1985) Conception Rates in Couples Where Autoimmunity to Sperm Is Detected. *Fertility and Sterility*, **43**, 739-742. https://doi.org/10.1016/S0015-0282(16)48557-2

[8] Bates, C. (1997) Antisperm Antibodies and Male Subfertility. *British Journal of Urology*, **80**, 691-697. https://doi.org/10.1046/j.1464-410X.1997.00379.x

[9] Mazumdar, S. and Levine, A.S. (1998) Antisperm Antibodies: Etiology, Pathogenesis, Diagnosis, and Treatment. *Fertility and Sterility*, **70**, 799-810. https://doi.org/10.1016/S0015-0282(98)00302-1

[10] Urry, R.L., Carrell, D.T., Starr, N.T., Snow, B.W. and Middleton, R.G. (1994) The Incidence of Antisperm Antibodies in Infertility Patients with a History of Cryptorchidism. *The Journal of Urology*, **151**, 381-383. https://doi.org/10.1016/S0022-5347(17)34954-6

[11] Heidenreich, A., Bonfig, R., Wilbert, D.M., Strohmaier, W.L. and Engelmann, U.H. (1994) Risk Factors for Antisperm Antibodies in Infertile Men. *American Journal of Reproductive Immunology*, **31**, 69-76. https://doi.org/10.1111/j.1600-0897.1994.tb00849.x

[12] Meinertz, H., Linnet, L., Fogh-Andersen, P. and Hjort, T. (1990) Antisperm Antibodies and Fertility after Vasovasostomy: A Follow-Up Study of 216 Men. *Fertility and Sterility*, **54**, 315-321. https://doi.org/10.1016/S0015-0282(16)53710-8

[13] Snick, H., Snick, T., Evers, J. and Collins, J. (1997) The Spontaneous Pregnancy Prognosis in Untreated Subfertile Couples: The Walcheren Primary Care Study. *Human Reproduction* (*Oxford, England*), **12**, 1582-1588. https://doi.org/10.1093/humrep/12.7.1582

[14] Vazquez-Levin, M.H., Marín-Briggiler, C.I. and Veaute, C. (2014) Antisperm Antibodies: Invaluable Tools toward the Identification of Sperm Proteins Involved in Fertilization. *American Journal of Reproductive Immunology*, **72**, 206-218. https://doi.org/10.1111/aji.12272

[15] Mahony, M. and Alexander, N. (1991) Opinion Site of Antisperm Antibody Action. *Human Reproduction*, **6**, 1426-1430. https://doi.org/10.1093/oxfordjournals.humrep.a137282

[16] Bandoh, R., Yamano, S., Kamada, M., Daitoh, T. and Aono, T. (1992) Effect of Sperm-Immobilizing Antibodies on the Acrosome Reaction of Human Spermatozoa. *Fertility and Sterility*, **57**, 387-392. https://doi.org/10.1016/S0015-0282(16)54851-1

[17] Haagen, E., Hermens, R., Nelen, W., Braat, D., Grol, R. and Kremer, J. (2006) Subfertility Guidelines in Europe: The Quantity and Quality of Intrauterine Insemination Guidelines. *Human Reproduction*, **21**, 2103-2109. https://doi.org/10.1093/humrep/del100

[18] Hunault, C., Habbema, J., Eijkemans, M., Collins, J., Evers, J. and Te Velde, E. (2004) Two New Prediction Rules for Spontaneous Pregnancy Leading to Live Birth among Subfertile Couples, Based on the Synthesis of Three Previous Models. *Human Reproduction*, **19**, 2019-2026. https://doi.org/10.1093/humrep/deh365

[19] Aronson, J.K. (2015) Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions. Elsevier, Amsterdam.

[20] Snijder, C.A., te Velde, E., Roeleveld, N. and Burdorf, A. (2012) Occupational Exposure to Chemical Substances and Time to Pregnancy: A Systematic Review. *Human Reproduction*, **18**, 284-300. https://doi.org/10.1093/humupd/dms005

[21] Lawson, C.C., Whelan, E.A., Hibert, E.N.L., Spiegelman, D., Schernhammer, E.S. and Rich-Edwards, J.W. (2011) Rotating Shift Work and Menstrual Cycle Characteristics. *Epidemiology* (*Cambridge*, *Mass*), **22**, 305. https://doi.org/10.1097/EDE.0b013e3182130016

[22] Bennett, D.A. (2001) How Can I Deal with Missing Data in My Study? *Australian and New Zealand Journal of Public Health*, **25**, 464-469. https://doi.org/10.1111/j.1467-842X.2001.tb00294.x

[23] IBM C (2016) IBM SPSS Statistics for Windows, Version 24.0. Armonk.

[24] Cui, D., Han, G., Shang, Y., Liu, C., Xia, L., Li, L., *et al.* (2015) Antisperm Antibodies in Infertile Men and Their Effect on Semen Parameters: A Systematic Review and Meta-Analysis. *Clinica Chimica Acta*, **444**, 29-36. https://doi.org/10.1016/j.cca.2015.01.033

[25] Zini, A., Fahmy, N., Belzile, E., Ciampi, A., Al-Hathal, N. and Kotb, A. (2011) Antisperm Antibodies Are Not Associated with Pregnancy Rates after IVF and ICSI: Systematic Review and Meta-Analysis. *Human Reproduction*, **26**, 1288-1295. https://doi.org/10.1093/humrep/der074

[26] Chamley, L. and Clarke, G. (2007) Antisperm Antibodies and Conception. In: *Seminars in Immunopathology*, Springer, Berlin, 169-184. https://doi.org/10.1007/s00281-007-0075-2

[27] Leushuis, E., van der Steeg, J.W., Steures, P., Repping, S., Schöls, W., van der Veen, F., *et al.* (2009) Immunoglobulin G Antisperm Antibodies and Prediction of Spontaneous Pregnancy. *Fertility and Sterility*, **92**, 1659-1665. https://doi.org/10.1016/j.fertnstert.2008.08.082

[28] Steures, P., van der Steeg, J.W., Hompes, P.G., van der Veen, F. and Mol, B.W. (2007) Intrauterine Insemination in the Netherlands. *Reproductive Biomedicine Online*, **14**, 110-116. https://doi.org/10.1016/S1472-6483(10)60772-9

[29] Elder, K., Wick, K. and Edwards, R. (1990) Seminal Plasma Anti-Sperm Antibodies and IVF: The Effect of Semen Sample Collection into 50% Serum. *Human Reproduction*, **5**, 179-184. https://doi.org/10.1093/oxfordjournals.humrep.a137065

[30] Francavilla, F., Romano, R., Santucci, R., Marrone, V. and Corrao, G. (1992) Failure of Intrauterine Insemination in Male Immunological Infertility in Cases in Which

All Spermatozoa Are Antibody-Coated. *Fertility and Sterility*, **58**, 587-592. https://doi.org/10.1016/S0015-0282(16)55268-6

[31] Agarwal, A. (1992) Treatment of Immunological Infertility by Sperm Washing and Intrauterine Insemination. *Archives of Andrology*, **29**, 207-213. https://doi.org/10.3109/01485019208987726

[32] Foundation, N.I.R. (2020) National IVF Numbers 1996-2016. https://www.degynaecoloog.nl/nuttige-informatie/ivf-resultaten