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Dear Colleagues,

We are delighted to be with you in the July issue of our journal. In our July issue, we have prepared scientific studies for you, thanks to the dedicated and diligent work of our editorial board and referees.

The articles that will be published are planned according to acceptance order. Referee and download status of the manuscripts are posted on our journal's web site. To guide the authors, the statistics tab of our journal website, acceptance, rejection, and assessment durations of the candidate articles are shared with the authors. No articles without the Ethical permission could be shared in our journal.

In the thirth volume you are reading right now, I would like to thank to the academics who accepted to be referees and assessed the articles. Lastly, I would like to congratulate all the authors whose articles have been published.

Dear colleagues, our utmost effort is to elevate our journal, which is a national treasure, to its deserved highest level. As editors of the journal, we are indebted to the independent referees who have participated in the editorial board and the evaluation process. With best wishes, we look forward to meeting you in our next issue.

Cordualy Yours…

Prof. Oya GÖKMEN, MD
Honorary Editor in Chief

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Original Article

DOI: 10.51271/JCOGP-00013

Morphological analyses of sperms causing severe male infertility with light microscopy, motile sperm organellar morphology examination and electron microscopy technics

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ABSTRACT

Aims: To evaluate abnormal sperm morphology by three different methods including light microscope, real-time motile sperm organelle morphology assessment at 8050x high magnification and electron microscope and to determine degree of effect on morphologic defects.

Methods: Patient cohort of this study was selected among males referring to Memorial Hospital assisted reproductive methods and genetics center and having morphological sperm defects causing severe male infertility such as megalohead, tail stump, globozoospermia and pinhead abnormalities. 20 patients having morphological sperm defects causing severe male infertility and 3 control patients. 4 patients with megalohead abnormality, 6 patients with globozoospermia, 8 patients with tail stump abnormality and 2 patients with total pinhead abnormality were included into study and 3 voluntary fertile males formed the control group

Results: In megalohead group, together with multi-flagellum structure, irregular and large sperm heads, pinhead sperm abnormalities have been found to be accompanied. In globozoospermia type I group, sperm head were observed to be round and lacking acrosome, while in type II group, the cone-shaped nucleus and a small amount of acrosome were observed. In tail-stump group, sperm with short and blunt-shaped tail were also found to have scattered microtubules and 9+0 structure rather than 9+2. In pinhead group, some sperm with the head were seen, even it was rare, and 9+2 microtubule structure was striking.

Conclusion: Beside the light and electron microscopic techniques, the motile sperm organelle examination can offer information about sperm quality in a simple and quick way and by the Intracytoplasmic Morphologically selected Sperm Injection (IMSI) developed through the use of sperm selected by this technique can contribute to the success of in vitro fertilization centers. We believe that sperm selection at high magnifications can increase invitro fertilization (IVF) pregnancy rates in patients with sperm morphology that causes severe male infertility.

Keywords: Male infertility, IMSI, severe sperm morphology

INTRODUCTION

Infertility which is described as inability to conceive after 1 years of unprotected intercourse affect about 15% of couples at the moment. The causes of infertility affect males, females and both genders equally about one third for each.[1] In addition to sperm count and motility, sperm morphological abnormalities are important among parameters causing male infertility.[2] Sperms of infertile males have prominent morphological alterations enough to change functional characteristics when compared to sperms of fertile males. Globozoopermia, pinhead, megalohead and stump tail are among the most important sperm morphological defects causing infertility.[3]

In the last two decades, despite lack of improvement in evaluation techniques for sperm concentration or motility, there are considerable advance is evaluation techniques for sperm morphology. Since the aim of morphological evaluation is to make in vivo and in vitro predictions about sperm function, a meticulous selection of criteria for evaluation is of great importance.[4] Currently, sperm morphology evaluated according to Kruger criteria is the most important parameter in detecting fertile and infertile male.[5] However, in most of the sperm abnormalities detected by using Kruger criteria minor defects may be overlooked. In addition, diagnosis by fixed and stained sperm samples at the same time may also be considered as another disadvantage. Thus, Bartoov et al.[6]

have developed a novel morphological evaluation method in order to make a detailed real time morphological evaluation of motile sperm cells. By this method called as motile sperm organelle morphology examination (MSOME), 6 organelles of sperm (acrosome, nucleus, post-acrosomal lamina, neck, midpiece and axoneme) are examined as unstained and real-time by using invert light microscope under 6300x-8050x magnification. Thus, evaluation of sperm morphology during ICSI procedures became possible.

By these types of studies, evaluating and/or revealing histological structure of sperms causing severe male infertility will be possible. As it is known morphological sperm defects are among important reasons effecting success of centers for assisted reproductive methods. In this study, we aimed to compare sperms of fertile males with morphological sperm defects causing severe male infertility (Megalohead, Tail stump, Globozoospermiaa [Round head], Dense Pinhead abnormalities) by examining sperms under light microscope, MSOME and ultra-structurally by transmission electron microscope (TEM). Thus, with this study we aimed to provide better understanding of sperm morphology and consequently to contribute to assisted reproductive methods.

METHODS

This study is the scientific study of Ferhat Cengiz master's thesis named "Morphological analysis of sperms causing severe male infertility with light microscopy, motile sperm organellar morphology examination and electron microscopy technics", registered at the National Thesis Center with the number 267264, dated 19.07.2010. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients signed the free and informed consent form.

Patient cohort of this study was selected among males referring to Memorial Hospital assisted reproductive methods and genetics center and having morphological sperm defects causing severe male infertility such as megalohead, tail stump, globozoospermia and pinhead abnormalities. 4 patients with megalohead abnormality, 6 patients with Globozoospermiaa, 8 patients with tail stump abnormality and 2 patients with total pinhead abnormality were included into our study and 3 voluntary fertile males formed the control group.

Evaluation of semen sample was performed immediately after the end of normal liquefaction period (20-30 minutes). Concentration, motility, and morphology parameters were evaluated and recorded into semen analysis pre-registration form. In addition to this, volume, agglutination, pH and if present, immature germ cells other than sperm, red blood cells, leucocytes and epithelial cells were evaluated. To assess sperm concentration, after liquefaction of semen the material was homogenized by pipetting it several times by using Pasteur pipette. 5-10 µl sperm obtained by micropipette was counted in Makler Counting Chamber (Makler® Counting Chamber - Israel) by using phase contrast microscope (Olympus CH 30, Tokyo, Japan) under 20x magnification and sperm count was determined as million per milliliter. Motility and progression evaluation was done by using light microscope (Olympus CH 30, Tokyo, Japan) under 20x magnification according to WHO criteria and percentage of total motility, progressive motility, slow progression, in situ motility and immotility was calculated by counting at least 100 sperms. Percentage value of motile sperms among 100 counted sperms was regarded as sperm total motility.

Semen sample liquidated after evaluation was homogenized by liquid broth (ALLgrad wash- Canada) in 1/1 ratio and was concentrated by centrifugation in 1000 rpm/min for 10 min (Heraus Megafuge 40- Germany). After removal of supernatant, it was homogenized by adding 0.25 ml liquid broth onto pellet. After obtaining 10 µl, a fine smear was prepared by dropping on a clean slide.

After dried in the air Spermac Stain (Spermac Stain-Fertipro-Belgium) procedure was applied. After drying, the sample was evaluated by light microscope under 100x magnification and by phase contrast microscope (Olympus Bx50, Tokyo, Japan) with immersion oil. At least 100 sperms were counted and small head, long head, tail abnormality, neck and mid piece abnormality, amorph sperm or sperm with multiple abnormalities and specific structural defects; megalohead, tail stump, Globozoospermia, pinhead abnormalities were recorded into the sperm morphology evaluation form as percentage and images of the findings were taken.

Fresh ejaculate was used as sperm source for MSOME. Sperm preparation appropriate for each sample was done. After preparation sperms were stored in 0,2 ml HTF solution as suspension at 37°C. For evaluation an amount that contains nearly 5000 sperm from the prepared semen sample was inseminated into 10 µl liquid broth droplet within 10% range prepared over sterile petri dish with glass base and covered with sterile paraffin oil. Sperm evaluation was done by Zeiss Axio Observer A1 invert microscope equipped with DIC objective and DIC condenser. For imaging 1.0 x camera adaptor and 1/3" Sony DxC-390P 3 CCD video attached to microscope and 19" Samsung LCD monitor were used. Total predicted magnification was calculated as 8050x. For general classification of semen samples MSOME criteria Bartoov's table was used. In MSOME 6 organelle (acrosome, nucleus, post-acrosomal lamina, neck, midpiece and axoneme) were examined and images of findings were taken.

Sperm samples were concentrated by centrifugation under 2700 rpm/min for 10 minutes for routine electron microscopes. The sample was fixed with 2.5% gluteraldehyde for 4-6 hours. To prevent disintegration of concentrated sperm in the following electron microscope follow up procedures it was embedded into 2% pure agar. Subsequently, follow up used for routine electron microscopic examinations was performed in Trakya University Medical Faculty Histology and Embryology department. To detect section region of the blocks semi-thin section were obtained (RMCMTx Ultramicrotom American) and stained by azure blue. Thin sections with 40-60 nm thickness from the determined areas were obtained, sections were stained by uranyl acetate and to increase contrast by Reynold's lead citrate stains. These sections were examined under Jeol 1010 electron microscope and images of findings were taken.

Statistical Analysis

In statistical analyses, we considered a p-value < 0.05 to be significant. We used Chi-square test for correlation analysis.

RESULTS

Control Group

In light microscope sperm heads were usually oval with 4.0-5.0 µm length and 2.5-3.5 µm width. Acrosomal region was well defined, consisting 40-70% of the head. Mid piece was straight in most of the sperms and its ratio relative to head length was 1.5-2.0 and it was axially attached to the head. Tails were straight, slender in the mid portion, uncoiled and nearly 40-50 µm long (**Figure 1a**). There were sperms with abnormal morphology along with sperms that were normal.

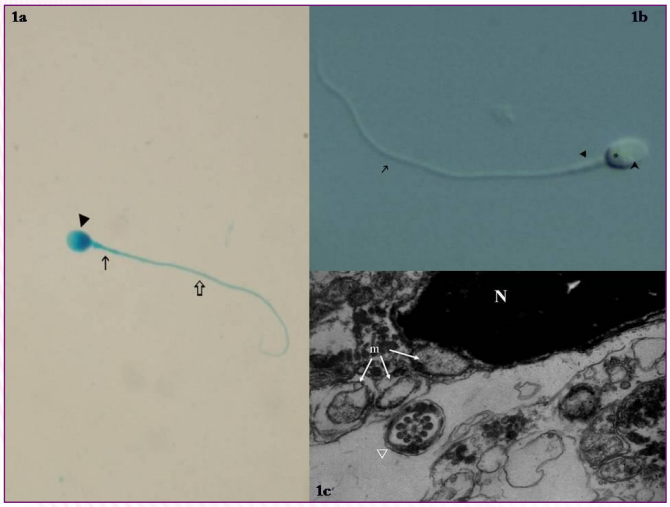

Figure 1. **1a.** Normal sperm appearance in control group: a well defined acrosomal region covering 50% of sperm head (◀). Mid-piece slender, long, axially attached to the head, contains no residual cytoplasm. (→). Straight, non-deformed, thin in mid portion, uncoiled and nearly 40–50 µm long tail is noticed (⇒). Spermac Stain, x1000 **1b.** Sperm appearance in control group: Small vacuoles less than 4% of sperm head is seen (▼). Nucleus is normal, symmetrical and oval (*). Neck axially attached to the head and doesn't contain residual cytoplasm(▲). A tail which straight, thin in the mid portion, uncoiled, having normal shape and dimension is noticed(→). MSOME, x8050 **1c.**Sperm appearance in control group: Nucleus is normal and includes mature chromatin (N), Mitochondria are normal and symmetrically located (m). In cross-sectional views tails containing microtubules that are in 9+2 design were noticed.(▽). Uranyl acetate-Lead sitrate, x50000

6 organelles of sperm (acrosome, nucleus, post-acrosomal lamina, neck, midpiece and tail) were examined by MSOME. Acrosomes were in the front side of head with proper structure and there was no vacuole within the nucleus. Neck was axially attached to the head and there was no residual cytoplasm. Mitochondria were located at neck properly. Tails were straight, slender in the mid portion, uncoiled and nearly 40-50 µm long. Nuclei were in proper shape with regular, symmetric and oval configuration (**Figure 1b**).

In electron microscope evaluation acrosomal cap region of the sperms were normal in shape, continuous and covering 50-60% of front part of the head with a dense content. Nuclei were normal in shape with mature chromatin. Axoneme structures in tails were in normal appearance. Fibrous sheath structures were appearing normal and as whole. In most of the microtubule structures that were observed 9+2 structure was present. Mitochondria were normal in shape and located symmetrically and regularly in both sides of the sperm neck (**Figure 1c**).

Megalohead Group

When evaluated according to Kruger criteria it was observed that most of the sperm heads were larger than normal size. In some patients large heads with regular structure in certain proportions were observed among sperms with normal size. Acrosomal cysts were seen in acrosomal region of some sperms. Within the sperms megalohead sperms along with pinhead sperms and tail problems were present. In some sperms there was irregular acrosomal regions covering sperm head and it was noteworthy that in some sperms mid piece wasn't axially attached to head. Residual cytoplasm and multiple tails with normal length were seen. Along with megalohead sperms double-head, double-tail sperms and morphologically indiscriminate sperms were present. There were sperms with amorph head and giant free head lacking tails (**Figure 2a**).

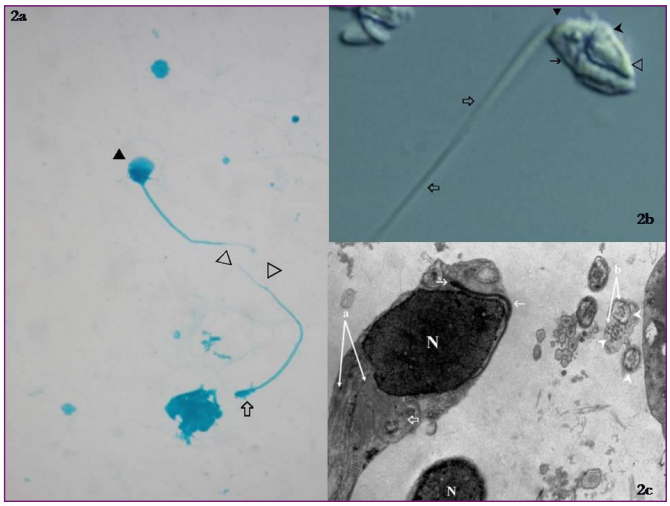

Figure 2. 2a. General appearance of Megalohead group: Megalohead sperms(⇒) were accompanied by pinhead sperms (▶). It's noticed that these sperms have tail abnormalities (□). Spermac Stain, x1000. **2b.** Sperm appearance in Megalohead group: Tail is not axially attached to the head (▶) and there are large residual cytoplasm (□). Straight tail structure is observed. (⇒). Abnormalities in acrosomal (□) and nuclear portions are noticed (▶). MSOME, x8050 2c. Sperm appearance in Megalohead group: Nucleus is large and includes mature chromatin (N). Acrosomal cap is observed in some areas of head but disrupted in some other areas (□). Residual cytoplasm is observed (⇒). There is deviation from 9+2 microtubule structure in axonemes. In longitudinal (a) and transversal (b) sections poliaxoneme structure is noticed (▶). Uranyl acetate- Lead citrate, x20000

Neck of the sperms evaluated by MSOME in the megalohead group weren't axially attached to head and were containing large residual cytoplasm. Mitochondrial distribution was irregular and there were multiple tails. Nuclei were usually amorph and configuration was distorted. High rate of vacuolization was observed in nuclear regions (**Figure 2b**).

In electron microscopic evaluation of this group nuclear structure was usually binuclear or large. Two nuclei not separated from each other in a single head was noteworthy. Acrosomal caps were in normal shape and were present in some parts of heads but on the other head disrupted in other parts with dense content. Residual cytoplasm was very frequently seen. Longitudinal and transverse sections revealed multiple tails. Deviation from 9 + 2 structure was seen in these axonemes. Mitochondrias were abnormal

in shape and Mitochondrial distribution was irregular (**Figure 2c**).

Globozoospermia Group

Light microscopic evaluation of this group revealed totally round heads without acrosomes. Mid piece was attached to the head axially and residual cytoplasm was noteworthy. Tails were straight, slender in the midportion, uncoiled and in normal length. Pinhead abnormality and amorph sperms were accompanying round head sperms. There were vacuoles in some of the round head sperms. Regional mitochondrial loss was seen in neck of most of the sperms. In another group of patients with type II defect there were acrososomal residues. Residual cytoplasm was rarely seen. Pinhead sperm abnormality was accompanying type II round sperms (**Figure 3a**).

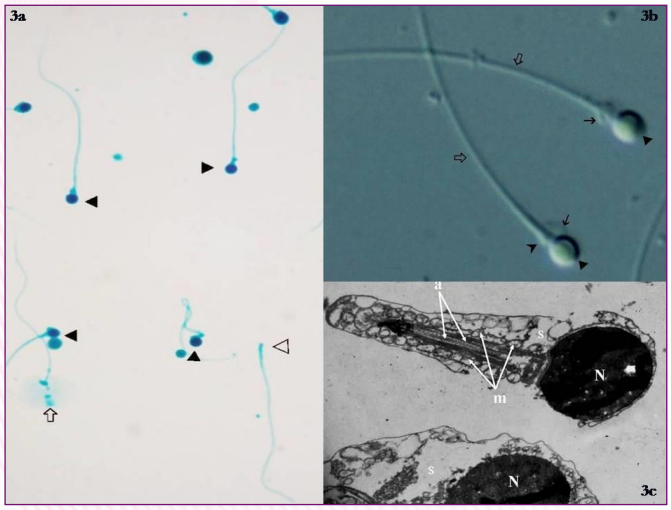

Figure 3. **3a**. General appearance of globozoospermia group: Evaluated sperm heads were totally round and were lacking acrosome (▶). Sperm with round head also accompanied by pinhead sperm abnormality (▽) and amorph sperms (⇒). Spermac Stain, x1000 **3b.** General appearance of globozoospermia group: Sperm heads were round and lacking acrosome (▶). Sperm neck contains residual cytoplasm (→), but there is no defect indicating lack of mitochondria or mitochondria disarrangement (➤). Tails are straight in shape, thin in the mid portion and uncoiled (⇒). MSOME, x8050 **3c.** Electron microscope appearance of globozoospermia group: Sperm nuclei are round and there is no acrosome (N). Axoneme structures are normal (a). Residual cytoplasm is observed in many sperms (s) Mitochondria are in normal shape and symmetrically located in both sides of neck (m). Uranyl acetate-Lead citrate, x20000

MSOME in Globozoospermia group has revealed sperm heads were round and lacking acrosomes. Neck was axially attached to the head and rarely contained residual cytoplasm. Mitochondria were regularly located in the neck region. However, in some sperms there were some disorderly conditions such as lacking or irregular mitochondria in the neck region. Tails were normal. In most of the sperm head a large and central vacuole was seen (**Figure 3b**).

Electron microscopic evaluation of Globozoospermia group has revealed round sperm heads without acrosomes. Nuclei were round and having condensed chromatin. Residual cytoplasm was very intense in sperms. In most of the sperm head a large and central vacuole was seen. Mitochondria were normal in shape and regularly and symmetrically located in both sides of the neck region. Axoneme structures were normal in shape, dynein arms and outer dense fibres were structurally normal. There sperms with normal microtubuler structure along with sperms deviating from 9+2 structure (**Figure 3c**).

Tail Stump Group

Evaluation of semen samples of this group revealed that some of the sperm heads were normal in shape but some other abnormal. However, abnormalities were seen in neck, mid piece and tail structures. Large residual cytoplasm was observed in some sperms. In many sperms tail was short and these were predominantly seen in a typical morphology which is short and thick tail. Free heads were frequently seen and rarely tails with normal length was also observed (**Figure 4a**).

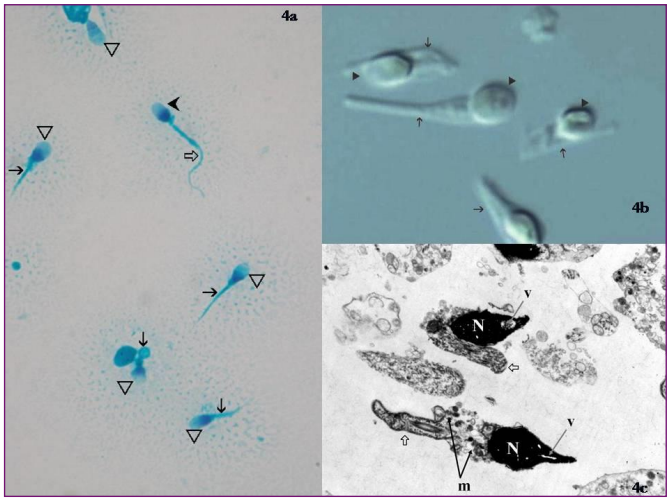

Figure 4. **4a.** General appearance of Tail stump group: Evaluated sperm heads are in normal (➤) and abnormal shape (▽). Tail morphology reveals usually a short tail (⇒), along with this, typical short thick tail shape of tail stump syndrome is noticeable (→). Spermac Stain, x1000 **4b.** General appearance of Tail stump group: In some evaluated patients sperm heads were found to be round (▶). Neck, mid-piece and tail characteristics of these sperms were observed to be abnormal. Accompanying short thick tail typical of tail stump syndrome is noticeable (→). MSOME, x8050 **4c.** Transmission electron microscope appearance of Tail stump group: Many of the evaluated nucleus were normal in shape, contained mature chromatin (N) and vacuoles (v). Dense and disarranged mitochondria were observed (m). Axoneme structures were found to be very short (⇒). Uranyl acetate-Lead citrate, x10000

Motility is meagre in tail stump syndrome thus using MSOME method in these patients is difficult. Thus, evaluation of these patients was only done by morphological analysis under higher magnification. MSOME has revealed acrosomes with normal structure in the sperm head and heads didn't contain vacuoles. Many necks were axially attached to the head and containing residual cytoplasm. There were sperms with free head in addition to sperms with short tails. Mitochondria were irregularly located within the sperm neck, there was lack of mitochondria in many sperm neck and there were disorders such as lacking or irregular mitochondria in the neck region. Some tails were attached to the head non-axially. In all tail stump samples sperm tails were short and these were predominantly seen in a typical morphology which is short and thick tail. Some sperms contained vacuoles and in some others sperm head was round and without acrosome (**Figure 4b**).

In the electron microscopic evaluation of tail stump group nuclei of sperms were normally shaped and having mature chromatin. In many sperms there wasn't any residual cytoplasm and mitochondria were intense and irregularly distributed. Fibrous sheath structure of sperms was disorderly and in pieces when it's available for evaluation. Acrosomal cap structure of many sperms was normal. Many axoneme structures were short. Observed

microtubule structures were irregularly distributed and having 9+0, 8+0 microtubule structure (**Figure 4c**).

Total Pinhead Group

In one of the patients in total pinhead group, sperm head couldn't be observed and in other patient only loosely attached sperm heads could be seen. There were variations in the neck, mid piece and tail parts of these sperms; however, they were usually structurally normal. Tail of sperms without head was straight. As a striking finding, there was residual cytoplasm at neck giving the impression of a head (**Figure 5a**).

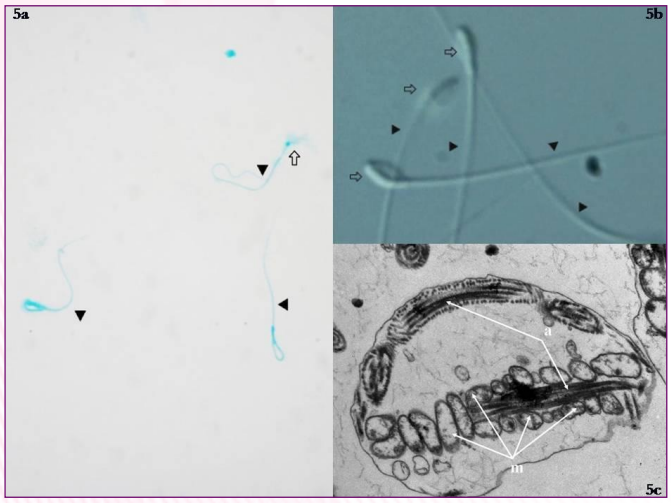

Figure 5: **5a.** General appearance of Total pinhead group: Sperms without head having tail that is straight, slender in the mid-portion, uncoiled and at normal length are observed. (▶). Residual cytoplasm is noticed at neck (⇒). Spermac stain, x1000 **5b.** General appearance of Total pinhead group: Sperms without head having straight tail structure (▶) and residual cytoplasm seems like head at neck region (⇒). MSOME, x8050 **5c**. Neck appearance in Total pinhead group: There is no nuclear content normal tail and several head ending, however axoneme structure is straight (a). Mitochondria are in straight and symmetrically located in both sides of neck (m). Uranyl acetate-Lead citrate, x30000

In MSOME there was sperm without head and with usually straight tail structure. Very rarely there were sperms with head non-axially and loosely attached to the neck. But in one patient residual cytoplasm giving the impression of a head at neck was noticeable (**Figure 5b**).

In the electron microscopic evaluation tail parts in longitudinal and transverse sections were noteworthy. Evaluated microtubular structure was 9+2. In patients normal tail structure occasionally ending with head was observed but there was no nuclear content. Mitochondria were symmetrically and regularly located within neck. Rarely in neck of some sperms there were findings relevant to lacking or irregular mitochondria. Axoneme structures were normal in general (**Figure 5c**).

DISCUSSION

Infertility is inability to conceive after 1 years of unprotected intercourse. Half of the issues involved with infertility are due to the man; but, in 30-50% etiology cannot be determined.[8] Currently semen analysis provides precious data relevant to male infertility and guidance for infertility treatment as the first test performed in male infertility.[9] Selection of a good-quality spermatozoon with normal morphology by using IMSI might be beneficial to embryonic development and to increase implantation and pregnancy rates. According to the majority of studies, it is not recommended to use IMSI routinely in the ART program. The couples with repeated implantation failures, patients with severe male factor infertility, advanced male and maternal ages are the populations who will have higher chances to conceive from IMSI. It is also recommended that diagnostic morphological evaluation of semen samples with high magnification is done before ICSI/IMSI procedure. Besides, according to the current knowledge, no prenatal or postnatal complications in the mothers and off- spring were reported following the IMSI procedure. The effectiveness of IMSI is still controversial mainly due to differences in inclusion criteria, stimulation protocols, seminal and oocyte qualities and many other confounding variables within the ART program. However, there is no doubt that the use of IMSI techniques can be helpful for some infertile couples to have a baby. [10]

It's known that morphological sperm abnormalities causing severe male infertility consist of megalohead, tail stump, Globozoospermia, total pinhead abnormality. The common result of ICSI procedure with these sperms are usually low fertilization rate, maldevelopment and/or late development of the fetus, high aneuploidy rate, low implantation and pregnancy rates. Since this precludes fertility substantially, it further decreases success rate of ICSI procedures performed on these patients.[2,3,11]

A well understood morphological pathology is important for guiding the treatment in centres using assisted reproductive method. However, there is no study evaluating all of the methods used for detecting above mentioned abnormalities at the same time. This study was designed to evaluate all of the methods used for detecting morphological sperm abnormalities causing severe male infertility at the same time, to evaluate relative superiority of these methods to each other and to answer the question of what's the best method to select the right sperm to increase chance of success before the ICSI procedure.

Currently WHO 2010 guideline is used as sperm morphology evaluation method; however, we used Kruger criteria in our study and evaluated sperm morphology accordingly.[7]

In the still most valid morphology evaluation, which is performed by Kruger et al.[13]; there should be a well-defined acrosomal region involving 40-70% of sperm head in the normal sperm. Mid piece should be long and slender and width should be less than 1 µm and its length should be 1.5X the head and it should be attached to the head axially. Residual cytoplasm may cover less than half of the normal head region. Tail should be straight, slender in the mid portion, uncoiled and nearly 45 µm long and at least 4% of the total sperms should be in accordance with this kind of sperm morphology. Sperm selection methods are an important challenge in assisted reproduction because most sperm characteristics cannot be tested, either in real time or in single cells referred to the ICSI procedure. Sperm selection under a magnification of ·400, in preparation for ICSI, allows the identification of major sperm morphological defects but does not provide information regarding the nuclear status of the sperm cell.[14]

In our study, sperm samples of fertile control group cases stained by Spermac stain were evaluated according to Kruger criteria and sperm morphology was found to be normal. Although there were some abnormal sperms, morphology of most of the sperms were normal or near normal.

In a study performed by obtaining images by digital imaging using invert light microscope under 6300x-8050x magnification by method described as MSOME, relationship between MSOME characteristics and ICSI outcome was assessed. Microinjection of sperms containing vacuoles was found to be correlated with early abortion and low pregnancy rates.6 In our Control group we observed that data obtained by MSOME was in accordance with the study of Bartoov et al.[6] Ability to use apparent normally shaped sperms is considered as a great advantage for ICSI procedure.

In publications studying ultra-structure of normal sperm in the usual description it was reported that in a single sperm totally enveloped by plasma membrane acrosomal cap is continuous and in normal position, shape, size and has intense content. It was observed that nucleus is in normal shape, has mature chromatin and sperm has no residual cytoplasm. Mitochondria is in normal shape and located regularly in both sides of the axoneme and there are nine peripheral microtubule pair along with two central microtubule structure (9×2+2).[15,16] In our electron microscopic evaluation we have observed that in the Control group acrosomal cap was in normal shape, continuous and its size was enough to involve 60% of sperm head from the anterior. Nucleus was in normal shape with mature chromatin and observed microtubule structures was 9+2. Mitochondria were in normal shape and located symmetrically in both sides of the neck. In our study we have observed that sperm ultra-structure was in accordance with the literature.

Megalohead described by Nistal et al.[17] is a very special form of sperm morphologic defects and is characterized by presence of low motility sperms, varying number of tail structure, irregular large sized heads. The same group have also reported that in cases having pinhead abnormality other morphological sperm abnormalities were also seen in varying proportions.

Kahraman et al.[11] have reported in their study that in megalohead sperm samples the most important morphological features are sperm with multiple heads and without tail and substantial amount of immature spermatid in ejaculate/testicular sperm extraction solution.

General evaluation of semen samples obtained from patients with megalohead sperm multiple tails, irregular large sized sperm heads, sperms with pinhead abnormality in most of the samples, amorph and irregular head shape along with acrosomal cysts in the acrosomal region were observed. In MSOME of megalohead group in our study nucleus was usually large, amorph and with distorted configuration and lots of sperms containing vacuoles were observed. In our study MSOME results were similar with the results of light microscopic examination. We suggest that the ability to use sperms near normal size observed in MSOME may provide a great advantage.

The high magnification approach is also of particular benefit when used in situations in which the identification of specific sperm organelles is required, such as the acrosomal components in cases of globozoospermia. Sermondade et al.[18] reported a successful pregnancy and healthy childbirth in a case of total globozoospermia after IMSI.

Chelli et al.[19] studied the chromosomal content of spermatozoa selected by IMSI in two cases of macrocephalic sperm head syndrome. FISH was performed in selected spermatozoa with normal-sized heads after IMSI selection. However, of the six spermatozoa that could be selected, all were aneuploid.[14]

Escalier has described a quantitative morphology for megalohead and multiple tailed sperm cells in 1983 by studying 6 infertile men.[20] In other electron microscopic studies about megalohead sperm cells several nuclei could be clearly distinguished within the head and it was suggested that this may occur due to defects arising during spermiogenesis I or spermatogenesis II stage of meiosis.[11] In our study, it was observed that in general, nuclear structure was double and large. Multiple tail structure is observed rather in longitudinal and transverse sections and deviation from 9+2 microrubule structure was observed in these axonemes. It was determined that results of our electron microscopic evaluation were in accordance with the literature.

In the study performed by Singh et al.[21] two sub types of Globozoospermia was described. Type I Globozoospermia is described as absolute absence of acrosom content. They reported lack of acrosome along with structural defects in axoneme, tail, mitochondria and microtubules. They have stated that in type II Globozoospermia acrosome residues were observed and there was a conic nucleus with surrounding cytoplasmic ringlets.[2,3] In our study, in type I Globozoospermia group it was observed that sperm heads were totally round and there was lack of acrosome in the head region. It was observed that residual cytoplasm was prominent and pinhead abnormality and amorph sperms were also observed. In type II Globozoospermia conic nucleus and a small amount of acrosome within the sperm was noteworthy. When evaluated by MSOME, in Globozoospermiaa sperm heads were round and lacking acrosome and large vacuoles observed in Globozoospermia were interpreted as an indicator of DNA damage in nuclear region. Bendayan et al.[22] demonstrated that sperm with vacuoles carry altered epigenetic marks (H3K4me3, H3K27me3) compared to sperm without vacuoles. MSOME/IMSI could be the first tool in assisted reproduction capable of reducing the risk of transmission of epigenetic problems through spermatozoa.[23]

It was reported that in type I Globozoospermiaa chromatin has spherical distribution and there is absolute absence of acrosome and there were structural defects in axoneme, tail, mitochondria and microtubules along with large vacuoles in the sperm head.[21] Electron microscopic evaluation of Globozoospermiaa group revealed lack of acrosome in the sperm head and a round and central vacuole. There were microtubules in line with 9+2 structure or deviating from 9+2 structure in compliance with previous studies.[24]

Chemes et al.[25,26] have described tail stump sperms and reported that they were totally immobile and were characterized by severe problems in sperm fibrous sheath organization. Tail is particularly short and thick thus it's called tail stump syndrome.[26] In our general evaluation of tail stump group, we have observed short tail along with short and thick tail structures. There were free heads and rarely tail with normal size. When MSOME was done in tail stump group it was observed that motile sperm percentage was low; thus morphological evaluation was performed under greater magnification and it was seen that tails were usually short and thick. In our study similar findings were observed when light microscope was used. However, it was considered that to select sperm with near normal long tail by Intracytoplasmic Morphologically *selected Sperm* Injection (*IMSI*) may be the method of choice.

Fibrous sheath dysplasia or tail stump syndrome was described in 6 different types in 2006 by Mitchell et al.[27] In electron microscopic evaluation of tail stump group in our study, it was observed that fibrous sheath structure was continuous in some regions on the other hand it's defective and in pieces in some other regions. Microtubule structures were deviating from 9+2 structure (9+0, 8+0) and microtubule structures were located in a disorganized way.

Perotti et al.[28] have stated that in an infertile patient most of the sperms didn't have any head and heads were detached. In the evaluation of total pinhead group in our study, we have observed sperms without head region but containing intense residual cytoplasm in the neck region. Additionally, there were sperms with head, though very rare. By MSOME in total pinhead group there were sperms with straight tail structure but without head and rarely sperms with head attached loosely to neck region. In our study similar findings were observed when light microscope was used. It was concluded that ability to use sperms with apparent head may create great advantage.

Chemes et al.[29] have shown in their study that pinhead sperms occur because of disorders related with midpiece attachment structure. Electron microscopic evaluation in our study revealed tail pieces in longitudinal and transverse sections. Observed microtubuler structures were in 9+2 structure. Sperm selection with MSOME parameters and IMSI can improve the embryo quality that was aimed using TLM and clinical outcomes in couples with male factor infertility. The data confirmed that patients with OAT and T took the most benefits from these advanced imaging systems of MSOME and TLM.[30]

There is still no consensus regarding the clinical value of IMSI. The contradictory results are caused by the lack of standardization of microscopy techniques used for ICSI and IMSI. Comparisons between IMSI and ICSI fertilization cycles may yield different results depending on the microscope setups used for ICSI and IMSI. When a high-quality system is used for ICSI that allows for visualizations of sperm vacuoles and obtained results are compared with IMSI, there may not be an apparent improvement. However, the clinics with a less advanced ICSI setup may experience improvements with the use of IMSI. This is why it is crucial to know what is being compared. In order to assess the influence of sperm vacuoles, the first step should be to set up the ICSI and IMSI systems and determine the size of vacuoles that can be visualized with each system.[31]

In our study; in addition to general morphological evaluation used in sperm defects causing severe male infertility we used MSOME for real time evaluation of sperm morphology and electron microscope and all of the methods gave results similar to previous studies irrespective of the evaluated groups and each evaluation method supported each other in respect of morphological evaluation findings. While it is thought that the selection of the best vacuoleless sperm at high magnifications, which was the opinion in the first years of the IMSI technique, can increase the success of the ICSI technique; We were of the opinion that the success rates of the samples with sperm morphological features that cause severe male infertility, which were examined within the scope of our study, could increase when the IMSI technique is used. The studies conducted so far support the initial views and results of our thesis. In addition, our study is the only IMSI study that examines sperm morphologies that cause severe male infertility.

Study Limitations: In our study, sperm morphologies that cause severe male infertility were examined, and no information was given about the embryo development and pregnancies of these patients.

CONCLUSION

As a conclusion, evaluating sperm morphology with MSOME which is a novel method in addition to light and electron microscopic methods may provide sufficient and important information in a short time. Also, in severe male infertility use of ICSI method developed by using sperms selected by this method may make significant contribution to success rate of centres using assisted reproductive method.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study is the scientific study of Ferhat Cengiz master's thesis named "Morphological analysis of sperms causing severe male infertility with light microscopy, motile sperm organellar morphology examination and electron microscopy technics", registered at the National Thesis Center with the number 267264, dated 19.07.2010.

Informed Consent: All patients signed the free and informed consent form.

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The management of the malposition of intrauterine devices at the tertiary center

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ABSTRACT

Aims: The malposition of intrauterine devices (IUD) is a major problem in contraception and this study aims to evaluate the surgical procedures used in the management of these cases

Methods: Patients who were operated on for malposition of copper T IUD between 2018-2021 were evaluated retrospectively. The cases were analyzed in 4 groups as followed; instrumental removal, hysteroscopic (H/S), laparoscopic (L/S), and laparotomic (LPT) procedure. The groups were compared in age, obstetric history, IUD insertion time, and intraoperative outcomes.

Results: There were a total of 39 cases and the groups consisted of instrumental removal (n=8), H/S (n=24), L/S (n=6), and LPT (n=1) procedure. In the H/S group, mean age (44±10) and duration of IUD use (10.1±7.5 years) were found to be significantly higher than the other groups (p=0.03 and p=0.001). Six cases (25%) in the H/S group IUD was in the uterine cavity while in 5 (20.8%) it was embedded in the endometrium and myometrium. In the L/S group the duration of IUD use was shorter (1.3±0.8 years) and the mean age (29±10) was lower and all cases were managed laparoscopically except in one case that was extracted after conversion to laparotomy.

Conclusion: Advanced age and prolonged IUD use are risk factors for embedded of the IUD in the uterine cavity in the hysteroscopy group, however, IUDs that reach the abdomen by ruptured uterus are detected at younger ages and earlier in IUD use, and minimally invasive methods are eligible surgical procedures for these cases.

Keywords: IUD, Malposition, Perforation, Hysteroscopy, Laparoscopy

INTRODUCTION

In Turkey, 49% of the women use a modern method of contraception, intrauterine devices (IUDs) are the second most widely used method with a prevalence of 14 %.[1] The term malposition covers a large range of different presentations either inside the uterine cavity such as low-lying, partially expelled embedded, horizontally displaced IUDs, or IUDs expelled outside the uterine cavity into the peritoneal cavity or neighboring organs after perforation of the uterus.[2-5] The malposition of the IUD may cause a serious problem in some cases that requires management with invasive procedures, including hysteroscopy, laparoscopy, and even laparotomy. In this study, the data and experience of a tertiary center are presented. In addition, case reports on the malposition of IUDs are also briefly compiled.

METHODS

The study group consisted of patients who had a malpositioned IUD that could not be removed at the family planning (FP) outpatient clinic of a tertiary center as an outpatient case and were hospitalized for intervention between 2018-2021. All the patients give informed consent approving the use of their medical data anonymously for medical research at admission as a part of the hospital protocol. This study was approved by Etlik Zübeyde Hanım Women's Health Research and Training Hospital Ethics Committee (Date: 26/02/2021, Decision No: 03/04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

As a part of the routine protocol of the FP when a malposed IUD is encountered in the FP, a gynecological examination and transvaginal ultrasonography are carried out. When the

IUD is found to be in the intrauterine cavity with or without observing the thread of the IUD, it is removed instrumentally with a hook, ring forceps, or alligator forceps. The patients are hospitalized if the IUD can not be removed instrumentally or if they are placed outside the uterine cavity. The patients who had their IUD removed at the FPC without requiring hospitalization or any other intervention were not recruited for the study. The flow chart of the study is presented in (Figure 1).

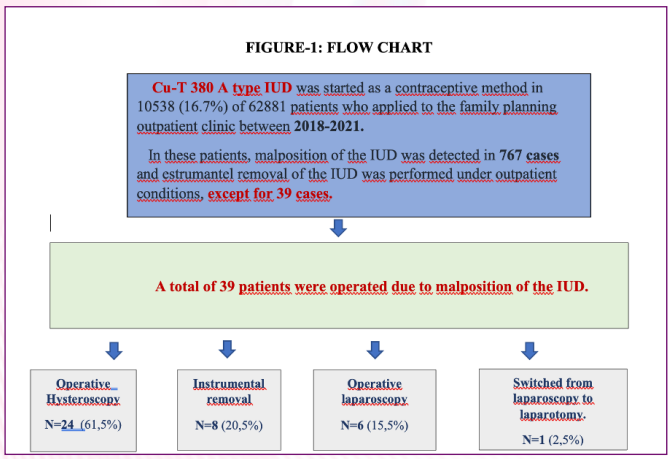

Figure 1: Flow chart of the study

The data about demographic characteristics, medical history, duration of the IUD use, laboratory tests, ultrasonographic findings, and the intervention and treatment protocol were extracted from the patient files.

Statistical Analysis

Statistical analysis was carried out with the SPSS 21.0 program. Categorical variables were evaluated with the chi-square test. Parametric and nonparametric tests were applied after the Shapiro-Wilk test was performed for the identification of data with normal distribution. One-way analysis of variance was performed for parameters with normal distribution and the Kruskal-Wallis test was used for nonparametric parameters. In the age parameter since the data were parametric, Tukey and Bonferroni tests, which are post hoc tests, were performed for the relationship between paired groups. For the duration of IUD insertion, since the data were non-parametric, the Mann-Whitney U test was performed in each pair to detect the difference in paired groups. A p-value of < 0.05 was accepted as statistically significant.

RESULTS

Between 2018 and 2021, the malposition of Cu-T 380 A IUD was detected in 767 patients, and removal was performed under outpatient conditions in the FP, except for 39 patients. In total, 39 patients were operated on due to the malposition of the Cu-T 380 A IUD. The patients were analyzed in 4 groups according to the procedure used for removal of the IUD; instrumental removal under anesthesia (n=8), hysteroscopic removal(n=24), laparoscopic removal (n=6), and laparotomy (n=1) groups

A total of 32 cases, had a failed trial of instrumental removal of the misplaced copper T IUD in the FP outpatient clinic. In the other 7 patients, the trial of instrumental intervention was not made at FP as either IUD partially was shown to be embedded in the myometrium by transvaginal ultrasonography or was placed in the abdominal cavity.

The general characteristics of these patients were given in Table 1. When the groups were compared there was no significant difference between demographic variables and obstetric histories such as the number of gravidities, previous cesarean section, spontaneous vaginal delivery, and abortion among the groups ($p>0.05$). The laparotomy group was not included in the statistical analysis, as there was only one case.

Table 1. Demographic characteristics, medical and obstetric history of the patients

Table 1	GROUPS			p value	Switched from laparoscopic to laparotomic procedure	Total cases
	Instrumental removal	Hysteroscopic procedure	Laparoscopic procedure			
	N=8 (20.5%)	N=24 (61.5%)	N=6 (15.5%)		N=1 (2.5%)	N=39
Age (Mean±Sd)	**39±8**	**44 ±10**	**29±10**	**0.03****	**42**	**41± 11**
Gravidae (Mean± Sd)	**3.25± 1.5**	**3.33 ±2.0**	**2.3 ±1.0**	**0.441***	**4**	**3.1± 1.8**
Previous Cesarean Section (Mean± Sd)	**1.8 ± 1.2**	**0.70 ± 0.9**	**0.5 ± 0.8**	**0.54***	**0**	**0.9 ± 1.0**
Previous vaginal delivery (Mean± Sd)	**1.1 ± 1.3**	**1.16 ± 1.6**	**1.5 ± 1.0**	**0.714***	**3**	**1.5 ± 1.4**
Previous abortion (Mean± Sd)	**0.25 ±0.46**	**0.9 ± 1.4**	**0.3 ± 0.5**	**0.214***	**1**	**0.7 ± 1.1**
Duration of IUD (years) (Mean± Sd)	**7.6 ± 3.3**	**10.1 ±7.5**	**1.3 ± 0.8**	**0.001***	**13**	**8.3 ± 6.8**
Radiological imaging	**Dislocated copper T IUD in the uterine cavity on TVUS**	**Dislocated copper T IUD or a part of, in the uterine cavity on TVUS**	**It is detailed in Table 3.**		**Two different copper T IUDs were seen in the uterine cavity on TVUS and in the abdomen on X-ray**	

* Kruskal-Wallis test ** One-way analysis of variance (ANOVA)
p<0.05 was considered statistically significant and the significant ones were bolded.
Abv: IUD; Intrauterine device, TVUS; Transvaginal ultrasonography, Sd; Standard deviation

In the hysteroscopy group, age (mean± SD;44 ±10) and duration of IUD use(mean± SD;10.1 ±7.5, Max-min;36-1 year) were found to be significantly higher than the other groups (p=0.03 and p=0.001, respectively).In the laparoscopy group, the duration of the IUD use was shorter (mean±SD;1.3±0.8, max-min;3-1 years) and mean age (mean±SD; 29±10) was found to be lower (p<0.05). For the relationship between the paired groups in the age parameter, there was a significant difference only in the laparoscopic and hysteroscopic groups (p=0.011), and those in the hysteroscopic procedure group were older. As for the duration from IUD insertion, when examining the difference in paired group, the laparoscopic group had a shorter duration of IUD use than the other two groups (p=0.007 versus instrumental removal, p<0.001 versus hysteroscopic procedure).

The location of the IUDs removed via operative hysteroscopy was given in **Table 2**. IUD was parallel to the longitudinal axis of the uterine cavity in 25% (n=6) of the patients while in four patients (16.6%) it was in the oblique-transverse position. Five of them (20.8%) had IUD observed in the right cornual area while in three (12.5%) it was in the left cornual area. In addition, a total of 20.8% was embedded in the uterine anterior(n=1), posterior (n=2), or isthmic (n=1) wall or inside the endocervical canal (n=1). Out of 24 patients, two patients had retained parts of the IUD that broke up during the instrumental removal of the misplaced IUD at another health center. In one patient, who was referred from another center after a failed trial of operative IUD removal, 3 separate tracts were observed in the uterine cavity during hysteroscopic observation and IUD extraction could not be performed, the patient was scheduled for another operation 3 months later after complete regeneration of the cavity and the IUD was removed successfully.

Table 2. Localization of the IUDs removed via a hysteroscopic procedure

	Number of cases (n)	Percent (%)	Additional features
Uterine cavity	6	25	In the longitudinal position
Right cornual area	5	20.8	IUDs arm or stem is present in two cases
Uterine fundus	4	16.6	In the oblique/ transverse position
Left cornual area	3	12.5	Concomitant uterine septum in one case
Posterior wall	2	8.3	Embedded
Anterior wall	1	4.1	Embedded
Isthmic level	1	4.1	Embedded
Endocervical canal	1	4.1	Embedded
Could not be reached (history of multiple instrumental attempts)	1	4.1	The presence of 3 different tracts in the uterine cavity due to previous operations

Abv: IUD; Intrauterine device

In six cases laparoscopy was required. And the findings in this group are briefly presented in **Table 3**. In case 6, the patient had a history of a spontaneous pregnancy with a misplaced IUD that could not be withdrawn as the string was not observed. This patient had a spontaneous vaginal delivery at full-term. However, the IUD was not expelled during the removal of the placenta after the delivery nor could be traced inside the uterine cavity by ultrasonographic examination. IUD was removed laparoscopically after being visualized abdominal X-Ray during the late post-partum period. During laparoscopy, the uterine wall was intact showing no sign of perforation. Also, radiological imaging results are presented in both **Table 1** and **Table 3**.

Table 3. Briefcase report of the laparoscopy group

Table 3	Results of radiological imaging	Localization of the IUD on laparoscopic observation	Location of the perforation area
Case 1	Hyperechoic appearance adjacent to the uterus on TVUS	A completely discarded IUD from the uterus and adhered to the posterior wall of the uterus	Not detected
Case 2	An IUD extending along the myometrium from the cavity to the serosa on TVUS	The IUD perforates the uterus from the posterior wall, the string is seen through the abdomen, and the remaining part of the partially expulsed IUD is embedded in the myometrium.	Posterior of the uterus
Case 3	There is no IUD in the uterine cavity on TVUS, but it was detected in the abdominal cavity on X-ray.	Embedded in the omentum.	Not detected
Case 4	There is no IUD in the uterine cavity on TVUS, but it was detected in the abdominal cavity on X-ray.	Embedded in the omentum.	The site of rupture was not detected, but the patient has an isthmocele and there was a suspicious area related to the perforation of this region during IUD insertion.
Case 5	An IUD extending along the myometrium from the cavity to the serosa on TVUS	The uterine perforation was observed during insertion and the IUD was removed laparoscopically	A perforated area in the left corneal area and minimal intra-abdominal coagulum were observed
Case 6	There is no IUD in the uterine cavity on TVUS, but it was detected in the abdominal cavity on X-ray.	An IUD that is freely located between the omentum	Not detected

Abv: IUD;Intrauterine device, TVUS;Transvaginal ultrasonography

The case that had a conversion to laparotomy after a failed trial of laparoscopic removal of IUD is presented: The patient was a 42-year-old asymptomatic woman who applied for IUD removal that was inserted 10 years ago and requested a new IUD. Her last delivery was 11 years ago and before that delivery she had an IUD inserted. She could not remember the removal of that IUD and presumably got pregnant with an IUD inutero. The IUD was neither removed during her last pregnancy nor expulsed after delivery. She had a new IUD inserted after this delivery. Based on her obstetric history an abdominal X-Ray was taken and a second IUD was observed in the abdominal cavity 5 cm superior to the left iliac crest. A laparoscopy was performed for IUD removal and tubal ligation as she requested a bilateral tubal ligation. The missing IUD could not be found during laparoscopic observation and

an intraoperative X-Ray was taken that demonstrated the presence of the IUD in the abdominal cavity (Figure 2). The operation was converted to laparotomy and the missing IUD was palpated and embedded into the thickened omentum. The IUD was completely covered with the omentum, IUD was removed from the omentum and the patient was discharged with full recovery.

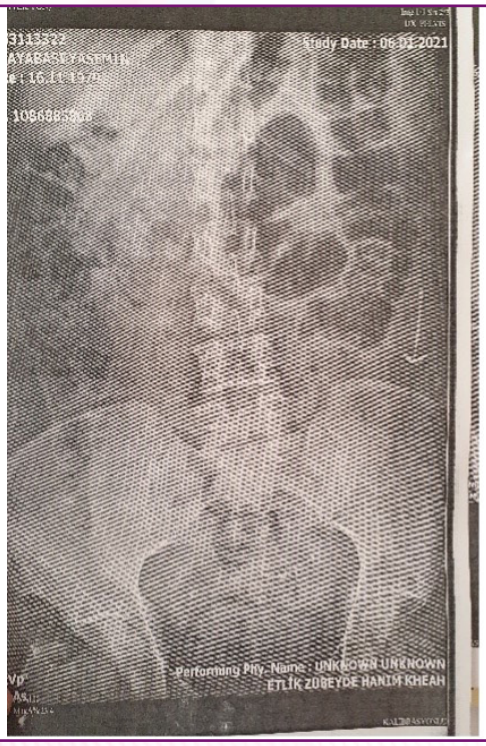

Figure 2. Radiographic appearance of the IUD located in the abdominal cavity

DISCUSSION

The intrauterine device is the most widely used method all around the world providing long-term contraception to around 106 million women and copper-bearing intrauterine devices are the most commonly used version.[6] The failure rate is very low and the IUD can be inserted at any time when the woman is proven to be not pregnant besides during the post-abortive and postpartum period in compliance with the medical eligibility criteria described by World Health Organization.[7]

IUD malposition can be diagnosed in asymptomatic patients during routine ultrasonography or a gynecological examination or when an asymptomatic woman attends the clinic with an unexpected pregnancy. Malposition of the IUD is categorized as expulsion, embedding, dislocation, perforation, and complete expulsion of the IUD from the uterine cavity. Expulsion is usually noticed by women unless it is expelled during heavy uterine bleeding and partial expulsion of the IUD is defined as a downward displacement of more than 2 cm from the uterine fundus.[5,8] Golightly et al.[8] suggested four different approaches for the treatment of an intrauterine misplaced IUD in asymptomatic women, from wait-and-see to removal of the IUD and switching to another method of contraception. The results of the studies about the risk of pregnancy in women with a partially expulsed IUD and clinical symptomatology are contradictory.[2-8] Even if the IUD is partially expulsed, embedded, and dislocated, their management may not always be this easy, and especially misplace IUDs due to uterine perforation may present with serious clinical findings.

Dislocated IUDs parallel to the longitudinal axis of the intrauterine cavity, even with only the string twisted into the endocervical canal, can be removed instrumentally by using a hook, ring forceps, or alligator forceps without the need for an additional surgical procedure.[8,9] Although insertion and removal of the IUD at the outpatient clinic are usually swift and tolerable for women, these procedures are sometimes affected by the patient's perception of pain and anxiety, and the clinician's experience and skills. The risk factors for increased pain scores with gynecological procedures include nulliparity, postmenopausal status, history of dysmenorrhea, anxiety, or expected high pain levels.[10,11] In this study, IUD removal was not performed in eight patients under outpatient conditions, and instrumental removal was required under anesthesia and sedation.

Hysteroscopic removal is a safe procedure for misplaced IUDs located in the uterine cavity in cases where ultrasound-guided removal fails. Asto and Habana[12] presented hysteroscopic IUD removal in 19 patients with a mean age32±9 years and the duration of IUD use was 5±10 years. In the presented study, the mean age (44 ±10) and duration of IUD use (10.1±7.5) were higher in the hysteroscopy group. hysteroscopy is a minimally invasive procedure and offers the advantage of short hospital stay, and minimal early, and late complications.[13] In the presented series, among 24 patients who required a hysteroscopic removal including two cases who had retained parts of the IUD inside the cavity, no complications occurred. While there were a total of 5 (20.8%) cases visualized as embedded in the myometrium during hysteroscopy, IUD was inside the cavity parallel to the longitudinal axis of the uterine cavity in six cases. Apart from these, IUDs were found to be in the transverse axis either in the cornual area (20.8%) or uterine cavity at the level of the fundus (16.6%).

Complete or partial uterine perforation related to IUD insertion is a rare but serious complication as IUD can damage the neighboring organs after being expelled into the abdominal cavity.[14] The incidence ranges between 0.4 per 1000 devices.[15] to 1.6 per 1000 insertions.[15] Among the presented seven cases that required laparoscopy (n=6) and laparotomy for IUD removal from the abdominal cavity, uterine perforation was detected only in three cases (33.3%) during the operations presumably due to the healing of the ruptured area and implying that the uterine perforation was not recent.

Various risk factors for the development of IUD malposition have been investigated by several researchers; the presence of a retroflexed uterus, uterine fibroids,[18] shorter uterine width,[19] and shorter uterine length,[15-19] were among the most frequent risk factors. In our series, only one patient had a uterine septum. However, the duration of the follow-up and the number of women who come for a regular follow-up affect the calculated incidence rate as some of the cases will not demonstrate any symptoms and will not come for regular follow-ups. After uterine perforation, 80% of the IUDs are observed to be embedded in the peritoneal space and 30% of the patients are asymptomatic.[20] In this study, a malposed IUD was found in the intra-abdominal cavity (66.6%) and adherent to the posterior wall of the uterus (33.3%). In the presented series, cases with laparoscopic

removal of IUD with an occult area of perforation had a shorter duration of the IUD use, these patients were younger, and the number of previous pregnancies was lower. Mosley et al.[21] analyzed 30 studies with 129 case reports on elective surgical removal of IUDs and reported that laparoscopy was the method of choice in 93% while in 22.5% of the cases, conversion to laparotomy was required. In the presented case series only one patient out of 7 cases with an intraabdominal IUD required laparotomy for IUD removal as the IUD was completely embedded between the layers of the omentum.

In some cases, uterine perforation and expulsion to the peritoneal cavity are recognized during insertion. The rate of perforation for Cu-IUD after a year of follow-up is 0.41 per 1000 insertions and this figure reached 1.6 per 1000 insertions when the study period was extended.[17-22] Within the first 6 months after delivery, the presence of breastfeeding, or amenorrhea, was the common factor observed in women with uterine perforation related to the IUD.[15,22] However, Braten et al.[2] did not identify early postpartum insertion (6–9 weeks postpartum) as a risk factor for malpositioning, however, the presence of leiomyoma increased the risk while having previous vaginal delivery lowered the risk.

The strength of this study is the clinical experience of a reference center in the treatment of malposition of IUD thus contributing to the literature with limited data on this subject, and identifying differences in minimally invasive approaches in cases where IUD removal failed in outpatient conditions. There are limitations as it is a retrospective study. **Table 2** shows the localizations of the malposition of IUD observed only with the hysteroscopic procedure. Even if the laparoscopic procedure is taken as a second group for the location of the most frequent rupture, statistical analysis could not be performed, since the cases are unique and only half of the group knew where the IUD ruptured and the others could not be detected. Also, due to the study's retrospective nature, conditions related to the timing of insertion, such as postpartum and post-abortion, were not examined.

CONCLUSION

This study emphasized the importance of clinical history and follow-up of women using the IUD, which is a cost-effective, easy-to-apply method, and how the surgical management would be, by presenting cases operated in a tertiary center. However, serious surgical procedures may be required for IUDs when rare complications and unusual conditions arise. This study found that the mean age and duration of IUD use were significantly higher in the hysteroscopy group than in the laparoscopy group. It has been shown that advanced age and prolonged IUD use are risk factors for embedded and dislocation of the IUD in the uterine cavity in the hysteroscopy group in this study, however, IUDs that reach the abdomen by ruptured uterus are detected at younger ages and earlier in IUD use in the laparoscopy group, and minimally invasive methods are eligible surgical procedures for the malposition of IUD

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Etlik Zübeyde Hanım Women's Health Training and Research Hospital Ethics Committee (Date: 26/02/2021, Decision No: 03/04).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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Polycystic ovarian syndrome review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age. It is characterized by a combination of hormonal imbalances, ovarian dysfunction, and metabolic disturbances. PCOS has significant implications for women's health, fertility, and overall well-being. This comprehensive review aims to provide an overview of PCOS, including its etiology, clinical manifestations, diagnosis, and management strategies.

Keywords: Infertility, insulin resistance, polycystic ovarian syndrome, PCOS,

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disease of reproductive-aged women with a lot of metabolic, reproductive, and psychological consequences. The pathophysiology of PCOS is complex, primarily caused by genetic mutations, hyperandrogenism, insulin resistance, persistent low-grade inflammation, and adipose tissue dysfunction. 2003 Rotterdam diagnostic classification is recommended, which requires two of the three: oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology[1]. Treatment options include lifestyle changes, pharmacological management such as combined oral contraceptives, metformin, antiandrogens, and combinations of them.

EPIDEMIOLOGY

PCOS is a common endocrine disorder in women of childbearing potential, with an estimated global prevalence of 5-15% using the Rotterdam Consensus Criteria.[1]

Depending on the diagnostic criteria being utilized, the prevalence ranges from 4-8% according to NIH/NICHD criteria to over 18% according to Rotterdam criteria.[2]

Besides the differences between diagnostic parameters, the level of occurrence varies by geographic (countryside vs. city) and personal factors (physical activity level, diet, etc.).[3] Some ethnic communities have been reported to have higher PCOS prevalence.[4] Han Chinese and Australian aboriginal populations are a couple of groups where PCOS has been researched.[4] There are racial and ethnic disparities in the prevalence of PCOS-related metabolic syndrome, which suggests the significance of dietary, climatic, or other lifestyle factors in the emergence of PCOS.[4] PCOS prevalence is higher among the races where obesity and insulin resistance are more common.[4]

Cosmetics that appear harmless, such as skin-whitening products, wrinkle creams, deodorants, sunscreen, and hair color, can disturb the hormonal balance, causing or exacerbating PCOS.[4]

PATHOPHYSIOLOGY

The pathophysiology of PCOS is complex and includes a wide range of abnormalities, mainly in the hypothalamic-pituitary-ovarian axis and insulin function. It involves a vicious cycle between hyperandrogenism, insulin resistance, persistent low-grade inflammation, and adipose tissue dysfunction (Table 1).

Also, genetic susceptibility and a strong correlation between several genes and pathways have been shown in PCOS pathophysiology. Genetic mutations, such as deletions, inversions, additions, and single nucleotide polymorphisms (SNPs) are potential contributors(Table 2).

Hyperandrogenism

Excessive levels of testosterone, androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone

sulfate (DHEAS) are one of the main causes of PCOS development.

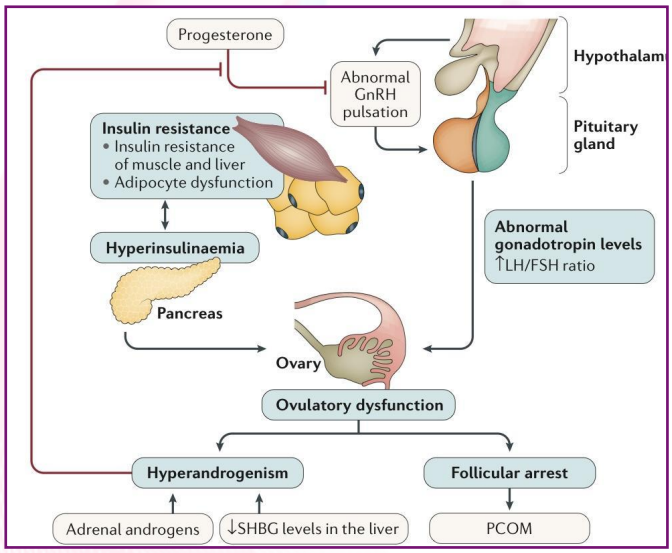

Table 1. Pathophysiology of PCOS[5]

FSH: Follicle stimulating Hormone, **GnRH:** Gonadotropin-releasing hormone, **LH:** Luteinizing Hormone, **PCOM:** Polycystic ovarian morphology

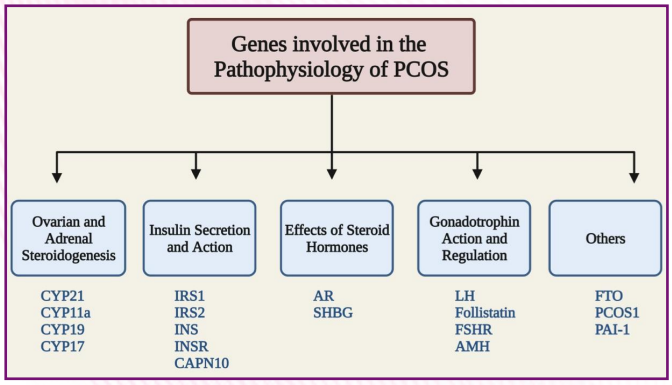

Table 2. Genes involved in the pathophysiology of PCOS[5]

CYP: cytochrome family p450; **IRS:** insulin receptor substrate; **INS:** insulin gene; **INSR:** insulin receptor; AR: androgen receptor gene; **SHBG:** sex hormone binding globulin; **FSHR:** follicle-stimulating hormone receptor; **LH:** lutein hormone e; **AMH:** anti-Mullerian hormone; **FTO:** fat mass obesity; **PAI-1:** plasminogen activator inhibitor 1; and **CAPN10:** caplain-10.

It is revealed that increased expression of several genes encoding steroidogenic enzymes causes exaggerated androgen synthesis in follicular theca cells.[6] Greater conversion of progestogen precursors to androgens caused by increased expression of CYP17A1 (the gene encoding the rate-limiting enzyme in androgen production) can be another contributor to the mechanism.[6]

An endocrine derangement in PCOS is the acceleration of GnRH pulsatile activity, which raises the frequency and pulse amplitude of LH over FSH, resulting in an increased LH/FSH ratio.[7] Interaction between high levels of LH and LH receptors promotes the proliferation of theca cells and furthermore contributes to the hyperandrogenic state.[8]

Despite the fact that the ovaries are the primary source of hyperandrogenism in PCOS, 20% to 30% of patients also have disproportionate adrenal androgen, caused by excessive ACTH secretion due to an imbalance in cortisol steroidogenesis.[9]

Insulin Resistance

Due to post-insulin receptor abnormalities, such as reduced glucose oxidation, impaired glucose phosphorylation, glucose synthesis and transport, insulin resistance is seen in PCOS patients.[10]

Insulin signaling is impaired in muscle due to increased serine phosphorylation of the insulin receptor and insulin receptor substrate 1 (IRS1).[11]

It is also shown that PCOS is linked to reduced GLUT4 (glucose transporter-4) expression as well as increased levels of oxidative stress in visceral adipose tissue, which had a direct correlation with insulin resistance.[12]

Hyperinsulinemia, caused by insulin resistance, increases androgen secretion from ovaries and adrenal glands, therewithal inhibits SHBG synthesis. Hence, the level of androgens increases. As can be seen, the production of insulin is greatly enhanced by androgen, but then androgen is further stimulated by insulin, creating an endless loop. In this regard, insulin resistance and metabolic problems are more prevalent in hyperandrogenic PCOS phenotypes.[13]

Chronic Inflammation

In many studies, it is revealed that chronic inflammation state contributes to the pathophysiology of PCOS. Inflammatory cytokines, especially tumor necrosis factor alpha (TNF-α) and interleukin beta (IL-β), play an important role.[14] Increased leukocyte count, C-reactive protein (CRP), IL-6, IL-18, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1 can also be seen.[15]

Recent studies showed that increased levels of advanced glycosylation end products (AGEs) and their receptors are other contributors to inflammation in PCOS.[16]

Adipose Tissue Dysfunction

Adipocytes and adipocyte activity are dysregulated in PCOS, favoring insulin resistance and subclinical inflammation even though women with PCOS may exhibit different distributions of fat or total BMI. It is demonstrated that women with PCOS appear to have larger adipocytes and decreased lipoprotein lipase activity.[17,18]

CLINICAL FEATURES

SYMPTOMS

PCOS affects both adolescents and adult women, which is a condition with a variety of distinct manifestations.[19] Patients apply to the clinics with various symptoms that affect their physical appearance and quality of daily life.

Immune and metabolic abnormalities are encountered due to chronic low-grade inflammatory state in PCOS.[20] Since recent years, the pathogenic function of immunological dysregulation in PCOS has been implicated in the alteration of several organ systems throughout the body, besides the female reproductive system.[20] This includes gynecological

symptoms such as oligomenorrhea, amenorrhea, and infertility as well as dermatological symptoms including hirsutism, acne, and alopecia.[19]

Oligomenorrhea / Amenorrhea

In the first one to two years following menarche, irregular menstruation is frequent.[21] The majority of girls experience normal monthly cycles by their fifth gynecological year as cycle variability gradually reduces over time.[21] To be identified as oligomenorrheic, an adolescent girl must have less than four menstruation periods in a year if she is in the first postmenarchal year, and fewer than eight menstruation periods if she is postmenarchal by 3-5 years.[21] Five years after menarche, criteria for adults (less than nine periods annually) are used.[21] It's significant to note that menstruation intervals longer than 90 days are unusual, even in the first year following menarche.[21]

If the cycle is disturbed, amenorrhea may develop. This condition can be either primary or secondary.[21] Secondary amenorrhea, also known as hypothalamic amenorrhea, is defined by the lack of menstrual periods for three or more consecutive months, whereas primary amenorrhea is the failure to achieve menarche due to chromosomal or structural abnormalities.[21]

Infertility

PCOS is the primary cause of infertility as a concern of public health, impacting 8–13% of women of reproductive age.[22] It has been suggested that ovarian disruption, a key mechanism in anovulation and infertility, is caused by androgen excess, insulin resistance, and hypothalamic-pituitary dysfunction.[22]

The development of primordial follicles, selection of a dominant follicle, and ovulation are all normal steps in the ovary's life cycle.[21] The disruption of this recurrence pattern in PCOS emerges.[21] Even if several follicles develop, none of them become dominant.[21] Ovarian ultrasound imaging can show the polycystic ovaries as atresia of the follicles become evident.[21]

Patients with PCOS frequently have more than 12 cysts that are 8 mm in size in the ovary.[23] This condition makes around 70% of females infertile.[24]

In order to manage reproductive functions in PCOS patients, lifestyle changes may be counted as the first non-pharmacological treatment option When all non-pharmacological options fail, ovulation induction can be provided with pharmaceutical agents such as letrozole, clomiphene citrate (CC), metformin, and gonadotropins. Women with PCOS and anovulatory infertility are typically treated with letrozole as their first option.

Hirsutism, Acne and Alopecia

Hyperandrogenism has clinical manifestations such as hirsutism, acne, and androgenic alopecia. It is stated that hirsutism is seen in 65-75% of PCOS patients.[24] Although it is uncertain if the prevalence of acne is much higher in these individuals than that seen in the general population, 15–25% of PCOS patients experience acne, and ethnicity has an impact on this prevalence.[24] In order to restore the menstrual cycle and cure acne and hirsutism in women with PCOS, hormonal contraception is frequently used, sometimes in combination with antiandrogens.[25]

COMPLICATIONS/OUTCOMES

Infertility, obstetrical problems, endometrial cancer, mental disorders, metabolic abnormalities such as obstructive sleep apnea, dyslipidemia, obesity, and type 2 diabetes mellitus (T2DM) are all more common in women with PCOS. These women also have a higher risk of ovarian cancer, venous thromboembolism, cardiovascular and cerebrovascular events, and stroke.[18]

Metabolic Abnormalities and T2DM

A bidirectional association exist between PCOS and excess adiposity, with PCOS itself appearing to predispose to weight gain while excess weight aggravates the underlying hormonal imbalance.[26] Up to 37% of women who are overweight have PCOS.[27] A longitudinal analysis using the Northern Finland Birth Cohort 1966 Study also found a link between PCOS and increased body mass index (BMI) around the age of 6 caused by early adiposity.[28]

Adipose dysfunction caused by invasion of macrophages, inflammatory state, and insulin resistance is linked to obesity [21]. In this regard, obesity increases the risks of cardiometabolic disease by aggravating hyperinsulinemia. But also it is shown that a large portion of PCOS-affected women exhibit basal and glucose-stimulated hyperinsulinemia as well as insulin resistance regardless of BMI.[18] Insulin resistance not only plays a significant role in the pathogenesis of PCOS but also severely impacts PCOS patients by increasing their risk of chronic illnesses including T2DM and cardiovascular disorders.[5]

Endometrial Hyperplasia

Persistent anovulation, unopposed action of estrogen, and the absence of inhibitory effects of progesterone cause endometrial hyperplasia, which is another complication of PCOS.[29] Prolonged exposure to unopposed estrogen along with little or no endometrial shedding can induce endometrial hyperplasia, which can eventually turn into endometrial cancer.[29]

Gestational Diabetes Mellitus (GDM)

Beyond its impact on fertility and menstrual irregularities, PCOS has been associated with various perinatal outcomes. Women with PCOS have an increased risk of developing gestational diabetes mellitus during pregnancy.[30] The hormonal and metabolic abnormalities associated with PCOS, such as insulin resistance and impaired glucose tolerance, contribute to the development of GDM.

Psychological Distress

PCOS-diagnosed patients are more likely to experience severe

psychological distress, decreased well-being, despair, and worries about their future health and ability to conceive.[31] Patients also experience anxiety, depression, changes in eating habits, sexual dysfunction, and dysmorphic disorders after diagnosis.

Programs for mindfulness meditation have grown in popularity over the past several decades and are now being used in clinical studies to lower stress and enhance psychological wellness in patients with a variety of medical illnesses.[31] The synthesis of adrenal androgens, which are generated by the adrenal glands as a direct response to psychological discomfort, can be decreased by mindfulness meditation.[31]

DIAGNOSIS

DIAGNOSTIC CRITERIA

After Stein and Leventhal described PCOS for the first time in 1935 in a case series of seven women with hirsutism, obesity, amenorrhea, and bilateral enlarged polycystic ovaries, different diagnostic criteria have been made.[32]

NIH Criteria

The first attempt to develop standard diagnostic criteria for PCOS was at the National Institutes of Health (NIH) international conference in the early 1990s.[33] PCOS diagnosis is made if patients have all of the following criteria after excluding all other conditions linked to hyperandrogenism or anovulatory infertility:

- Oligo-anovulation,
- Clinical and/or biochemical signs of hyperandrogenism.

Using the NIH definition, the prevalence of PCOS has remained stable at 5-8%.[34]

Rotterdam Criteria

In 2003, experts gathered in Rotterdam (Netherlands) at a meeting sponsored by the European Society of Human Reproduction (ESHRE) and the American Society for Reproductive Medicine (ASRM) and agreed on new criteria.[2] PCOS diagnosis is made if patients have two of the following:

- Oligo-anovulation,
- Clinical and/or biochemical signs of hyperandrogenism,
- Polycystic ovarian morphology (PCOM) on ultrasonography.

As a result, several studies found that the prevalence of PCOS was up to three times higher than when the 1990 NIH criteria were used for diagnosis.[35]

According to the Rotterdam criteria, PCOS cases are divided into four phenotypes (depending on whether the three diagnostic criteria are present or not) as seen in the **Table3.**

Table 3. Phenotypes of PCOS

	Oligo-anovulation	Hyperandrogenism	PCOM
Phenotype A	+	+	+
Phenotype B	+	+	
Phenotype C		+	+
Phenotype D	+		+

PCOM:Polycystic ovarian morphology

AES Criteria

In 2006, the Androgen Excess Society (now known as the Androgen Excess-PCOS Society) asserted, that a PCOS diagnosis should be made if patients have all of the following criteria [36]:

- Clinical and/or biochemical signs of hyperandrogenism,
- Ovarian dysfunction, including oligo-anovulation and/or PCOM,
- Exclusion of other androgen excess-related disorders.

As a result, phenotype D based on the Rotterdam criteria was no longer considered PCOS.

These several diagnostic criteria have contributed to clinical uncertainty, hence the NIH held an evidence-based methodology workshop on PCOS in 2012, and it is advised to use the broader Rotterdam criteria with phenotypic specification.[35] Despite being the most widely used classification, using the Rotterdam criteria has not yet gained worldwide acceptance.

CLINICAL DIAGNOSTIC APPROACH

Menstrual periods that last more than 35 days or fewer than 21 days defined as amenorrhea requires further investigation in patients.

Hirsutism, alopecia, and acne are clinical symptoms of hyperandrogenism. Given that, only 60% of PCOS patients exhibit symptoms of hyperandrogenism, the diagnostic criteria for hyperandrogenism were expanded to include biochemical signs.[36] Regarding the ideal biochemical test for androgen excess, there is not a full consensus. The amount of SHBG has no impact on the assessment of free T, in contrast to total T. Measuring free T, total T, or calculating the androgen index is suggested.[37] It is strongly advised against doing tests for AMH, FSH, or insulin levels.[37]

To be able to say polycystic ovarian morphology, at least 25 small follicles (2 to 9 mm) must be found in the ovary.

PCOS can be difficult to diagnose in adolescents. Since anovulatory menstrual periods in the first several years postmenarche and also large polycystic ovaries can be seen, using classical diagnostic criteria is not reliable.[38]

TREATMENT

The patient's characteristics will determine the management strategy and optimum therapeutic option in PCOS patients. Infertility treatment, menstrual cycle control, weight loss, or alleviation from hyperandrogenic symptoms such acne, hirsutism, or androgenic alopecia may be counted as the symptomatic relieve in PCOS management. Pharmacological treatments and surgical procedures are both available for PCOS.

Lifestyle Modifications

The initial therapy suggestion emphasizes proper nutrition and physical activity regimens, especially for PCOS patients who are overweight or obese.[21]

Even modest weight loss with changing eating habits in obese women with PCOS improves biochemical reproductive outcomes, insulin resistance indicators, adiposity, and its distribution.[39] 2013 clinical practice guidelines from the Endocrine Society recommend using exercise therapies to treat obesity and overweight in PCOS patients.[4]

Combined Oral Contraceptives

The functional cysts associated with PCOS might go away on their own. However, certain cysts have the potential to burst and bleed, which can cause sudden, intense discomfort in the lower abdomen.[4] The combined oral contraceptives (COCPs), when used for six months, reduce hyperandrogenism and regulate menstrual cycles by inhibiting ovulation and cyst formation.[39]

COCPs also reduce androgens, raise SHBG levels, prevent conception, and maintain the integrity of the endometrial structure.[39] The available data indicate that there are no appreciable changes in body weight or glucose tolerance associated with COCP use in adult women, although there are increases in total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations.[39]

Although it is important to take risk factors into account such as hypertension, obesity, clotting history, and smoking, there is no evidence to show that women with PCOS who use oral contraceptives have more cardiovascular events than women in the general population.[39]

Metformin

Metformin is an insulin sensitizer that is frequently used to treat insulin resistance in PCOS patients. When it comes to reducing body weight, metformin is comparable to lifestyle changes, but it works better when it comes to lowering androgen levels. In comparison to lifestyle adjustments alone, the combination of metformin plus lifestyle changes provides increased quality of menstrual periods, reduced BMI, subcutaneous adipose tissue, and glucose levels in PCOS patients. It also has a mild to moderate impact on lowering cholesterol levels and relief of insulin resistance.[40]

Clomiphene citrate (CC) alone or in combination with metformin is advised for treating infertility in PCOS. There is proof that metformin has an advantage over placebo and CC alone in terms of pregnancy and ovulation rates. Therefore, rather than continuing with CC alone, especially in PCOS patients who are CC-resistant, CC might be coupled with metformin.[41,42] However this is also accompanied by a rise in multiple pregnancies (5-8%) and ovarian hyperstimulation syndrome (1%).[42]

Antiandrogens

Spironolactone, flutamide, and finasteride are antiandrogens that slow the development of new terminal hairs, which can be used to treat symptomatic complications of hyperandrogenism due to PCOS. Antiandrogens prevent the development of the external genitalia of male fetus, necessitating the use of very effective birth control at the same time. A very uncommon adverse effect of spironolactone is hyperkalemia.[21]

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Sudden infant death syndrome

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ABSTRACT

Sudden infant death syndrome (SIDS) is a type of sudden and unexpected infant death, a term that encompasses both deaths from SIDS and ultimately all unexpected infant deaths with a determined cause. 1 Between 27% and 43% of 3500 sudden unexpected infant death cases in the USA annually are due to SIDS. 2, 3 A number of other terms are used in pediatrics to describe sudden and unexpected deaths. Sudden unexpected death of an infant can be used interchangeably with sudden unexpected infant death, and sudden death in youth (ventricular arrhythmias; VAs) refers to such death in any child 19 years of age or younger. Sudden unexplained early neonatal death is limited to infants who die within the first week of life and is usually congenital. anomaly is caused. Sudden intrauterine unexpected death syndrome refers to stillbirths for which postmortem examination cannot identify a cause, and sudden unexpected death in epilepsy is unexpected death in a person with epilepsy (excluding trauma or suffocation) for which postmortem examination does not reveal an anatomical or toxicological cause.

Keywords: Pediatric, sudden infant death syndrome, death

SUDDEN INFANT DEATH SYNDROME

Sudden infant death syndrome (SIDS) is a type of sudden and unexpected infant death, a term that encompasses both deaths from SIDS and ultimately all unexpected infant deaths with a determined cause.[1] Between 27% and 43% of 3500 sudden unexpected infant death cases in the USA annually are due to SIDS.[2,3] A number of other terms are used in pediatrics to describe sudden and unexpected deaths. Sudden unexpected death of an infant can be used interchangeably with sudden unexpected infant death, and ssudden death in youth (ventricular arrhythmias; VAs) refers to such death in any child 19 years of age or younger. Unexplained sudden infant death is usually in the first week of life and is due to a congenital anomaly. Sudden intrauterine unexpected death syndrome refers to stillbirths for which postmortem examination cannot identify a cause, and sudden unexpected death in epilepsy is unexpected death in a person with epilepsy (excluding trauma or suffocation) for which postmortem examination does not reveal an anatomical or toxicological cause.

EPIDEMIOLOGY AND RISK FACTORS

SIDS is the leading cause of death for infants aged 1 month to 1 year. SIDS rates have dropped significantly from 130.3 deaths per 100,000 live births in 1990 to 38.7 deaths per 100,000 live births in 2014 2. This significant decrease is largely attributable to safer sleep practices promoted by the American Academy of Pediatrics “Back Sleep” and “Safe Sleep” campaigns, and to a lesser extent the classification of deaths from asphyxia or sleep drowning separately from SIDS; peaks at 2 to 4 months and is seen in 60% of male infants6. There are ethnic differences, with Asian Americans at lower risk and African Americans and Native Americans at higher risk mothers of SIDS victims are more often under 20 years of age, overweight, unmarried, use drugs, and have few prenatal and postnatal checkups prenatal and postnatal maternal smoking increases the incidence of SIDS. SIDS is more common in the winter months when the baby is awake, with 30-50% signs of acute respiratory tract infection.

Sleep position has received great attention as a modifiable SIDS risk factor. Prone position is associated with an odds ratio of 4.92 for the SIDS. In clinical studies, infants in the prone position have been found to rebreathe exhaled air and experience hypercarbia.[7] Additionally, infants normally dissipate heat from their heads, and prone sleep can prevent heat loss, thereby exacerbating hyperthermia, another risk factor for SIDS.[8] Many babies succumb to SIDS when with a babysitter.[9] Most of these babies are in the prone position. It happens when some babies are first placed in the prone position, and researchers have suggested that these babies have poor strength and tone in their neck muscles. Side sleeping is also considered a risk factor for SIDS and is not recommended. Because of these observations regarding the prone position, the American Academy of Pediatrics has recommended supine sleep for normal infants since 1992,

and in 2011 published a paper addressing specific sleep-related issues. The supine sleeping position does not increase the risk of aspiration in infants with GI reflux and should also be applied to premature infants, even in neonatal intensive care units, when they are medically stable. Infants should be placed in a cot, bassinet or crib (instead of an adult bed) on a firm mattress and protected from overheating. bed sharing; not recommended especially when baby is under 3 months old, parent smokes, excessively tired or using sedatives (especially alcohol) or using soft surfaces such as sofas or beds with soft mattresses. 4 Prone sleep, bed sharing, sleeping in a place other than a cot or bassinet were associated with 92.2% of SIDS deaths.[10] Sofas are a particularly dangerous sleep environment, generating sleep-related infant mortality.

Swaddling, a common practice to minimize crying and colic, has been shown to increase the risk of SIDS, especially in prone sleepers and especially in babies older than 6 months.[12] High ambient temperature can also contribute.[13] Pacifier use,[14] breastfeeding,[15] and vaccines[16] are protective against SIDS. It has not been shown to prevent SIDS.[17]

If a case does not meet the SIDS criteria, between 1% and 5% of cases of sudden unexpected infant death can be attributed to infanticide.[18] Familial "SIDS" cases increase the possibility of abuse. Traumatic head injuries, bruises, long bone fractures, rib fractures, internal bleeding, evidence of physical neglect or blood around the nose suggest abuse. [19] It is very common for SIDS victims to have a risky sleeping position. A SIDS death without these factors may raise suspicion of abuse. Similarly, channelopathies are a common cause of unexpected sudden infant death that must be excluded before death can be determined to be SIDS.

A registry system has recently been developed to gather accurate and comprehensive information on all sudden deaths in pediatric patients and to better understand the epidemiology and risk factors of both SIDS and sudden unexpected infant death.[20]

PATHOPHYSIOLOGY

Although the exact cause of SIDS is not known, it is thought to be multifaceted. intrathoracic Some autopsy features appear to be relatively consistent among infants succumbing to SIDS, including petechial hemorrhages, thyromegaly, encephalomegaly, microcardia, uncoagulated blood in the heart, kidney growth retardation, empty bladder, and rectum.' The hypothesized mechanism of SIDS, an infant's underlying vulnerability, a critical developmental period, and exogenous includes interaction between stressors— triple risk theory of SIDS. [21]

A genetic basis for infant vulnerability has been studied extensively recently. Although no single genetic locus has been identified for SIDS, the 10-fold increased risk among siblings of SIDS victims suggests a genetic component. Recently, the interleukin-10 gene promoter polymorphism has been associated with SIDS and sudden unexpected death associated with infection. Brain biomarkers ergothioneine, nicotinic acid, succinic acid, adenosine monophosphate and azelaic acid have been associated with SIDS and can predict SIDS. [22] Recent research on the brains of babies who died from SIDS ; medullary, including abnormal firing, synthesis, radiation and clearance shows the presence of serotonergic (5-hydroxytryptamine) pathology[23,24] and morphological differences[25,26] in the brainstem and hippocampus. This likely leads to an inadequate response to hypoxemia. autonomic Dysfunction has also been suggested to play a role.[27]

Infancy may represent a critical period for hypoxia, a possible contributor to SIDS. In general, infants are more likely to have apnea, sustained desaturation, and poor ventilation control. Newborns less than one month old have a better anaerobic capacity to survive and the ability to raise their partial arterial oxygen pressure with one breath. The rarity of SIDS in this age group supports a ventilator theory. Studies looking at babies at various altitudes have found an increased risk of SIDS, especially in children living at altitudes higher than 8,000 ft. [28]

Prenatal and perinatal nicotine exposure can be seen as an example of environmental stressors. nicotine hypercapnia It is hypothesized that it blunts ventilation responses and reduces central respiratory chemoreception by altering the expression of serotonin receptors.[29] The fact that supine sleep significantly reduces the incidence of SIDS suggests that the researchers enabled them to take a closer look at how sleep might affect the autoregulation of respiratory and cardiac centers. Supine sleep is likely to increase sympathetic tone and decrease REM sleep, both thought to reduce the risk of adverse autonomic events.[30,31]

CLINICAL FEATURES

In general, SIDS victims apply in one of two ways: ineligible for restitution or potentially responding to resuscitation measures. If there is no history of environmental hypothermia, rigor mortis, living Infants with a reticularis, PH 46 and significantly reduced core temperature should not be resuscitated. However, warm infants with apnea and no pulse may benefit from resuscitation attempts. of SIDS Regardless of presentation, take a thorough history and perform a complete physical examination. Important questions include a full description of conditions, caregivers, recent illness, prenatal and birth history, maternal and family miscarriage or other infant mortality, and family history of metabolic disease. For epidemiological information, documenting the sleeping position, sleeping location, when and by whom the baby was last seen alive, when and in what position the baby was found, and whether bed-sharing is included, helps the forensic officer. Examination of the infant may not reveal the cause or may show subtle but relevant signs of trauma such as facial bruising, petechiae, blood in the nose or mouth, or a ruptured frenulum that raises suspicion of trauma. rectal temperature and rigor The presence of mortis or bruising will help the forensic examiner determine an approximate time of death.

The families of babies with non-resuscitative SIDS are very emotionally demanding. One of the greatest responsibilities of the physician is to inform, advise and educate the family. The family often wants to spend time with the deceased baby. In general, once death has been declared, the infant's body should not be manipulated or photographed unless authorized by the forensic officer. If the family wants hand

or footprints, inkless pads should be used and this should be documented in the medical record. Do not remove any catheter or tubing inserted during the resuscitation attempt. If the presence of the tube bothers the family, the tubes can be cut from the skin to make it appear less obvious. Unless otherwise directed by the coroner, the family may keep the deceased infant in a private setting, but the family is allowed to spy.

In most jurisdictions, victims of sudden and unexplained deaths should be reported to the coroner as soon as possible. Treating physicians must complete a form notifying death, but not sign the official death certificate, as the cause of death will not be known until after the coroner's investigation is complete. SIDS is technically a post-mortem diagnosis, and sudden unexpected infant death is a more appropriate term for emergency room registration (although not included in the 10th revision of the International Classification of Diseases). If blood samples have been taken, keep the samples in the lab for later access by the forensic officer. Once death is reported, the physician is not authorized to perform postmortem sampling or radiography unless directed by forensic medicine.

Dysfunction associated with a prolonged QT interval or Wolff-Parkinson-White syndrome has been reported in sudden unexpected infant death, 32 autopsies found an accessory atrioventricular tract in 20% of cases of 'SIDS'. Up to %35 abnormal results on post-mortem cardiac canal testing.[33] One If a heart abnormality, particularly a channelopathy, is found, testing of family members can be life-saving, and this is a concrete example to encourage families to emphasize the importance of autopsy.

A home site survey is usually done. Some jurisdictions have infant mortality teams that fully assess the circumstances surrounding the unexpected death of young infants. If the physician believes that the baby is a victim of SIDS, the family should be informed about this, but should be told that the autopsy report is awaited for final confirmation. Involving a primary care provider who can follow up on the autopsy and stay in touch with the family is of paramount importance, The hospital chaplain or social worker can provide additional support and a pastor's counseling may be needed, especially in cases where autopsy laws conflict with the family's religious doctrine prior to the funeral. For infants who need perimortem baptism, this will ideally be done by a pastor, but can also be done by a medical care provider if the pastor is not present. Some states also require reporting to organ procurement agencies.

One of the recurring themes expressed by mothers of SIDS victims when interviewed is self-blame." Eliminating interactions that exacerbate this emotion is an important principle in the treatment of SIDS, while preserving the need for a thorough investigation.

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Letter to the Editor

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Rise and fall of 17 alfa-hydroxyprogesteronecaproate

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Dear Editor;

Low progesterone levels during early pregnancy is one of the factors that is related with threatened abortion. 17 alpha-hydroxyprogesterone caproate (17-OHPC), a synthetic progestogen, was first approved in 1956 to treat a variety of gynecological and obstetric conditions in pregnant women, including threatened abortion and preterm birth. 17-OHPC is a selective progesterone receptor agonist and is prepared for intramuscular (im) use in oil solution. 17-OHPC is licensed under the brand name Delalutin in USA and Proluton in Europe. High-dose (250 mg/mL intramuscular load) 17-OHPC was widely prescribed to pregnant women in the USA and Europe in the 1950s and 1960s. In October 1973, the U.S. Food and Drug Administration (FDA) reported the lack of significant evidence for the use of 17-OHPC for threatened abortion prevention and raised concern about the association of 17-OHPC with fetal congenital heart defects.[1] Then, all pregnancy-related indications were removed from the label, citing the possibility of teratogenic effects associated with systemic use and 17-OHPC was marked as Category D in pregnant women in 2009 by FDA.[1]

As a part of the Accelerated Approval Program, the FDA reapproved 17-OHPC in February 2011 under the name Makena for pregnant women with a history of spontaneous preterm birth, based on a randomized trial by Meis et al.[2] published in 2003. Meis et al showed a reduction in the incidence of preterm birth at 37 weeks. Use of IM 17-OHPC 250 mg weekly between 16/20 weeks to 36 weeks is recommended by the guidelines for prevention of preterm birth in women with a previous history of preterm birth. In 2009, detailed analysis of the Meis study by Calda[3] noted a statistically insignificant increase in fetal deaths and stillbirths among women using 17-OHPC. In 2007 Rouse[4] reported no improvement in the reduction of preterm births in twin pregnancies with the use of 17-OHPC. Similarly, Combs[5] reported no improvement in preterm delivery and neonatal delivery in twins and triplets with the use of 17-OHPC. Embryo-fetal toxicity related with 17-OHPC were demonstrated in two experimental studies on rhesus monkeys and rodents.[6] Maternal effects of 17-OHPC came under spotlight. two studies reported a higher incidence of abnormal glucose testing and gestational diabetes in women receiving 250mg 17-OHPC weekly while one study reported no increased risk.[7,8]

As a part of accelerated approval of 17-OHPC, FDA needed a confirmatory trial. A multi-center, randomized, double-blind, vehicle-controlled clinical trial (PROLONG Trial) was conducted on women with singleton pregnancies who had a history of spontaneous preterm delivery during their previous pregnancies. PROLONG Trial failed to show any reduction in preterm delivery before 35 weeks and neonatal morbidity and mortality.[9] As a result FDA approal of Makena was withdrawn.[9]

Although the drug is drawn form the market the questions about fetal long term effects are still in the spotlight. A recent publication by Murphy et al.[1] published in 2020 raised concern about the possible link between inutero 17-OHPC exposure and cancer risk in the offspring.[1] After analyzing mother-child records who took antenatal care at e between 1959 and 1966 and the Cancer registry, out of 18,751 offsprings 1% (n=234) were found to be exposed to 17-OHPC in-utero mostly during the first trimester due to threatened abortion. The median follow-up period was 45.9 years. Among the exposed 234 offsprings, 23 were diagnosed with cancer. Two of the cancer cases were diagnosed during childhood (age <18 years) and 21 in adulthood (age ≥18 years). As a result, compared to the offsprings not exposed to 17-OHPC, offsprings exposed had an increased risk of any cancer (adjusted Hazards Ratio: 1.99, 95% CI 1.31, 3.02). Exposure in the first trimester was associated with an increased risk of cancer (adjusted hazard ratio, 2.57; 95% confidence interval, 1.59e4.15), and the risk increased with the number of injections (1e2 injections: adjusted hazard ratio, 1.80; 95% confidence interval, 1.12e2.90; 3 injections: adjusted hazard ratio, 3.07; 95% confidence interval, 1.34e7.05). Late

exposure in the second or third trimester increases the risk in male (adjusted hazard ratio, 2.59; 95% confidence interval, 1.07e6.28) but not for the female (adjusted hazard ratio, 0.30; 95% confidence interval, 0.04e1.11) offspring. The risk of colorectal, prostate, and pediatric brain cancer was higher in the offspring exposed to 17-OHPC in the first trimester than the offspring not exposed. Most of the patients evaluated were born in the 1960s and the preparation was just being used and many pregnant women received repeated high-dose treatment. This study demonstrated that exposure to 3 or more injections, especially in the first trimester of pregnancy, increased the risk malignancy and late exposure increased the risk of the male gender.

The limitations of the Murphy et al.[1] is its retrospective design and the limited number of the analyzed cases and confounding factors. Prospective studies that will clarify the precise mechanisms contributing to cancer risk would probably take years. However, in the meantime, these findings raise significant concern regarding the use of 17-OHPC during pregnancy. New progesterone formulations such as vaginal progesterone are compared to 17-OHPC and show more favourable results.[10] However further studies with new formulations and different routes of delivery are requirred for an evidence-based recommendation for prevention of preterm delivery when different formulations are concerned.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was not required for this letter

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