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Role of intra-abdominal hypertension in the development and outcome of ovarian hyperstimulation syndrome

Aleksei Petrenko

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ROLE OF INTRA-ABDOMINAL HYPERTENSION IN THE DEVELOPMENT AND OUTCOME OF OVARIAN HYPERSTIMULATION SYNDROME

Doctoral thesis report presented by:

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To apply for the degree of: Doctor of Medicine from the University of Barcelona

Directed by:

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CERTIFIES:

That the thesis entitled « **ROLE OF INTRA-ABDOMINAL HYPERTENSION IN THE DEVELOPMENT AND OUTCOME OF OVARIAN HYPERSTIMULATION SYNDROME**» has been prepared, under his direction, by **ALEKSEI PETRENKO**, to apply for the degree of **Doctor of Medicine** from the **University of Barcelona**.

And, for the record, they sign this document, at the request of the petition of interests.

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May, 18th, 2022, Barcelona

To my parents worked the whole life as school teachers
and raised hundreds of students

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Index

Abbreviations

- ACS: abdominal compartment syndrome
- APD: anteroposterior diameter of the abdomen
- APP: abdominal perfusion pressure
- ARDS: acute respiratory distress syndrome
- ART: assisted reproductive technology
- AsI: ascites index
- BMI: body mass index
- Cab: abdominal wall compliance
- FSH: follicle-stimulating hormone
- GnRH: gonadotropin-releasing hormone
- HC: hip circumference
- hCG: human chorionic gonadotrophin
- IAH: intra-abdominal hypertension
- IAP: intra-abdominal pressure
- ICU: intensive care unit
- IL: interleukin
- IVF: in vitro fertilization
- LH: luteinizing hormone
- LMWH: low-molecular weight heparin
- OHSS: ovarian hyperstimulation syndrome
- OV: ovarian volumes
- PCOS: polycystic ovary syndrome
- RCOG: Royal College of Obstetricians and Gynaecologists
- TNF-α: tumor necrosis factor α
- TS: transverse diameter of the abdomen
- VEGF: vascular endothelial growth factor
- WC: waist circumference
- WSACS: World Society on Abdominal Compartment Syndrome

Articles that compose the Doctoral Thesis

Doctoral Thesis is presented in article compendium format. The thesis consists of five articles:

ARTICLE 1

Petrenko AP, Castelo-Branco C, Marshalov DV, Salov IA, Shifman EM. Ovarian hyperstimulation syndrome. A new look at an old problem. Gynecol Endocrinol. 2019 Aug;35(8):651-656. doi: 10.1080/09513590.2019.1592153. Epub 2019 Apr 2. PMID: 30935259.

It is located in the second quartile according Citescore (Scopus) and in the third quartile of the specialty of Obstetrics and Gynecology (position 54/83), according to the Journal Citation Reports 2020®.

ARTICLE 2

Petrenko AP, Castelo-Branco C. Perspective Advices in the Management of Ovarian Hyperstimulation Syndrome. J Gynecol Women's Health. 2019: 16(1): 555926. DOI: 10.19080/JGWH.2019.16.555926.

It is located in the fourth quartile of the specialty of Obstetrics and Gynecology, according to the Journal Citation Reports 2020®.

ARTICLE 3

Petrenko AP, Castelo Branco C, Marshalov DV, Salov IA, Kuligin AV, Shifman EM, Chauke SS. Alternative strategies for the management of ovarian hyperstimulation syndrome, the role of intra-abdominal hypertension control. Gynecol Endocrinol. 2020 Mar;36(3):197-203. doi: 10.1080/09513590.2019.1683822. Epub 2019 Oct 31. PMID: 31668111.

It is located in the second quartile according Citescore (Scopus) and in the third quartile of the specialty of Obstetrics and Gynecology (position 54/83), according to the Journal Citation Reports 2020®.

ARTICLE 4

Petrenko AP, Castelo-Branco C, Marshalov DV, Kuligin AV, Shifman EM, Nesnova ES. Assessing the Usefulness of Severity Markers in Women with Ovarian Hyperstimulation Syndrome. Reprod Sci. 2021 Apr;28(4):1041-1048. doi: 10.1007/s43032-020-00339-8. Epub 2020 Oct 15. PMID: 33063288.

It is located in the first quartile according Citescore (Scopus) and in the beginning of the second quartile of the specialty of Obstetrics and Gynecology (Ranking position 30/83), according to the Journal Citation Reports 2020®.

ARTICLE 5

Petrenko AP, Castelo-Branco C, Marshalov DV, Kuligin AV, Shifman EM, Nesnova ES, Batsunova MO. Are anthropometric data a tool for determining the severity of OHSS? Yes, it could be! BMC Women's Health. 2022 May 10;22(1):155. doi: 10.1186/s12905-022-01701-5. PMID: 35538521; PMCID: PMC9092801.

It is located in the first quartile according Citescore (Scopus) and in the beginning of the second quartile of the specialty of Obstetrics and Gynecology (Ranking position 40/83), according to the Journal Citation Reports 2020®.

Thesis summary

Papel de la hipertensión intraabdominal en el desarrollo y evolución del syndrome de hiperestimulación ovárica

Introducción

El síndrome de hiperestimulación ovárica (SHO) es la complicación yatrogénica más grave y potencialmente mortal asociada con las técnicas de reproducción asistida (TRA). El SHO moderado o grave puede complicar del 3 al 10% de todos los ciclos de TRA, con una incidencia de hasta el 20% en mujeres de alto riesgo. Por lo general, el SHO se desencadena por la acción de la gonadotropina coriónica humana y se atribuye principalmente a la secreción ovárica excesiva del factor de crecimiento endotelial vascular y otros factores angiogénicos, que aumentan la permeabilidad vascular y provocan la fuga de líquido hacia el tercer espacio. El SHO se caracteriza por la presencia de ovarios aumentados de tamaño con hipovolemia y hemoconcentración, incluyendo en los casos más graves ascitis, hipercoagulación, insuficiencia renal e incluso fallo multiorgánico en los casos críticos.

En las guías clínicas actuales en los casos en los cuales el SHO require cuidados intensivos solo se formulan recomendaciones de terapia sintomática. Esto último es debido a la falta de una comprensión clara de la fisiopatología del cuadro, lo que origina que sea imposible llevar a cabo un tratamiento efectivo desde el punto de vista patogenético. En la última edición de la guía del Royal College of Obstetricians & Gynecologists (RCOG) «El manejo del síndrome de hiperestimulación ovárica, guía Green-top, @ 5» (2016), la presión intraabdominal (PIA) se menciona en dos de tres indicaciones de paracentesis; sin embargo, no existen recomendaciones para su seguimiento. No se han registrado nuevos datos sobre la terapia intensiva para el SHO en la última década.

La progresión de la ascitis y el agrandamiento de los ovarios en el SHO conducen a un aumento de la PIA y, en formas graves y críticas, pueden causar el síndrome compartimental abdominal (SCA) y la disfunción orgánica grave asociada.

Una comparación de la fisiopatología y el cuadro clínico indica que los síntomas del síndrome de hiperestimulación ovárica grave y la disfunción orgánica asociada son casi idénticos al síndrome de hipertensión intraabdominal (HIA). Una tríada clásica, que incluye trastornos respiratorios, disminución del retorno venoso y restricción de la perfusión interna, está presente en pacientes con síndrome de hiperestimulación ovárica grave y síndrome de hipertensión intraabdominal.

Hipótesis de trabajo

La hipertensión intraabdominal puede desempeñar un papel en el desarrollo de formas graves de SHO y en sus complicaciones. El SHO moderado y severo con disfunción orgánica tendría la misma fisiopatología y características clínicas que el síndrome de hipertensión intraabdominal; por lo tanto, el tratamiento de las formas moderada y severa de SHO debería incluir los principios de la terapia para el síndrome de hipertensión intraabdominal.

Objetivos

Analizar los registros de historia clínica, laboratorio y factores de riesgo funcionales para el desarrollo de formas graves de SHO.

Estudiar los índices de presión intraabdominal en mujeres con varios grados de SHO y determinar su valor clínico.

Estudiar la dinámica y relación de indicadores de volumen ovárico, ascitis y presión intraabdominal con diversos grados de severidad de SHO.

Evaluar la utilidad de diversos indicadores antropométricos en la determinación de la gravedad del SHO.

Desarrollar indicaciones e indicadores adicionales para paracentesis basados en los datos de los presentes estudios.

Evaluar el valor diagnóstico de la hipertensión intraabdominal como criterio de gravedad del SHO.

Evaluar la utilidad de la hipertensión intraabdominal para predecir la progresión y los resultados del SHO.

Demostrar una relación plausible entre los cambios observados en la hipertensión intraabdominal con la efectividad del tratamiento.

Material y métodos

En este estudio se incluyeron un total de 76 mujeres infértiles que estaban en programa de fecundación in vitro y presentaban SHO. Todos ellos fueron admitidos en el Departamento de Ginecología del Hospital Clínico número 1 de la ciudad (Saratov, Rusia) que lleva el nombre de Yu.Ya. Gordeev. Se registraron datos antropométricos, de laboratorio y clínicos en todos los sujetos incluidos. El rango de edad de los participantes del estudio fue de 20 a 40 años y el índice de masa corporal (IMC) fue de 16,9 a 24,1 kg/m2.

El SHO se clasificó de acuerdo con las guías del RCOG. Por lo tanto, los pacientes se distribuyeron en cuatro grupos según la gravedad del SHO: SHO leve (grupo I, n = 25), SHO moderado (grupo II, n = 25), SHO grave (grupo III, n = 21) y SHO crítico (grupo IV, n = 5). La PIA se midió 4 [RIC, 3–5] días después de la administración de gonadotropina coriónica humana (GCh) en caso de SHO temprano y 17 [RIC, 13–19] días después de la activación de GCh en caso de SHO tardío. Todas las mujeres ingresadas con el diagnóstico de SHO fueron consideradas para su inclusión en el estudio. Se excluyeron aquellos que voluntariamente se negaron a participar.

Procedimientos

Todas las mujeres inscritas se sometieron a un examen clínico que incluyó altura, peso corporal, circunferencia abdominal, evaluación de deshidratación, edema, frecuencia cardíaca, frecuencia respiratoria, presión arterial y diuresis. En todos los casos se realizaron pruebas de laboratorio de rutina. Se registraron datos antropométricos y clínicos en todos los sujetos incluidos. El diámetro anteroposterior del abdomen (DAP) y el diámetro transverso del abdomen (TS) se midieron con un pelvímetro. Se calculó la relación DAP/TS.

Se realizó medición ecográfica del tamaño ovárico y líquido libre pélvico y abdominal (Accuvix XG [Samsung MEDISON Co. Ltd. Corea]) utilizando sensores sectoriales de 3,5 MHz. El volumen ovárico (VO) se estableció utilizando la fórmula del elipsoide prolato (alto × ancho × profundidad × 0,523).

El índice de ascitis (IAs) se determinó mediante ultrasonido junto a la cama y fue la suma de las mediciones de las bolsas verticales más profundas de líquido ascítico que se encuentran en cada uno de los cuatro cuadrantes abdominales.

La PIA se midió a través de un catéter de Foley utilizando un transductor de presión.

Análisis estadístico

Los datos se analizaron utilizando un paquete de software basado para computadora personal (SPSS 26.0, SPSS Inc. Sede, 233 South Wacker Drive, 11th Floor, Chicago, IL 60606, EE. UU.). Se utilizó la prueba de Shapiro-Wilk para determinar la distribución normal de la muestra. Los datos de las variables que no se distribuyen normalmente se dan como la mediana [rango intercuartílico]. La homogeneidad de las varianzas dentro del grupo se evaluó mediante la prueba de Levene. Se utilizó la prueba de Kruskal-Wallis para analizar las diferencias entre grupos. Los resultados estadísticamente significativos fueron seguidos por pruebas U de Mann-Whitney con ajuste de Bonferroni para detectar diferencias de subgrupos. Se utilizaron los coeficientes de correlación de Spearman para comprobar la asociación entre variables continuas. Todas las pruebas de probabilidad fueron bilaterales y un valor de $p < 0,05$ se consideró significativo.

Resultados obtenidos

Como era de esperar, el IAs aumentó progresivamente y tendió a ser el más alto en la etapa más sintomática de SHO (prueba de Kruskal-Wallis, $p < 0,001$). La mediana de IAs fue significativamente menor en pacientes con SHO moderado (197 mm [RIC, 140-235]) en comparación con SHO grave (285 mm [RIC, 276-321]; $p < 0,001$) o SHO crítico (320 mm [RIC, 310-346]; $p < 0,001$). Sin embargo, no hubo diferencias significativas en IAs entre los grupos de SHO grave y crítico. De igual manera, el VO mostró un aumento significativo. La mediana de VO en los casos de SHO leve (307 ml [RIC, 132–392]) fue significativamente diferente de la del moderado (500 ml [RIC, 441–561]; $p < 0,001$), grave (578 ml [RIC, 533–611]; $p < 0,001$), y SHO crítico (600 ml [RIC, 487-704]; $p < 0,001$).

Los estudios de PIA demostraron diferencias significativas entre los grupos, analizadas mediante la prueba de Kruskal-Wallis ($p < 0,001$). Al comparar cada dos grupos, se encontró que la mediana de la PIA del grupo de SHO leve (4,0 mmHg [RIC, 3,0–6,5]) era significativamente más baja que la del grupo moderado (12,0 mmHg [RIC, 11,0–13,0], $p < 0,001$), severo (16,0 mmHg [RIC, 14,5–18,0], $p < 0,001$) y grupos de SHO crítico (25,0 mmHg [RIC, 24,0–27,0], $p < 0,001$). Como se evidenció anteriormente, el deterioro del estado clínico se asocia con un aumento significativo de VO, IAs e PIA. La mediana de IAs fue significativamente mayor en pacientes con insuficiencia respiratoria (298 mm [RIC, 278-316]) en comparación con sujetos sin disnea (239 mm [RIC, 192-280]; $p < 0,01$). Del mismo modo, la PIA en mujeres con insuficiencia respiratoria (17,75 mmHg [RIC, 16,50-24,50]) fue significativamente diferente de la de pacientes sin disnea (11,0 mmHg [RIC, 5,25-13,75], $p < 0,001$). Se encontró que la mediana de la PIA en mujeres con distensión abdominal, náuseas o vómitos (13,5 mmHg [RIC, 12,0–17,0]) era significativamente más alta que en personas sin molestias abdominales (3,5 mmHg [RIC, 2,0–5,0], $p < 0,001$). La oliguria se asoció con un aumento considerable de IAs (289 mm [RIC, 271–316]) y PIA (17,0 mmHg [RIC, 14,50–19,25]) en comparación con la función renal normal (mediana de IAs: 196 mm [RIC, 140–235]), PIA mediana—8,5 mmHg [RIC, 4,0-12,0] $p < 0,001$). Como anticipábamos, hubo una fuerte correlación positiva entre la VO y la PIA (r de Spearman = 0,699, $p < 0,001$). Además de eso, el PIA mostró una correlación positiva significativa con el IAs (r de Spearman = 0,695, $p < 0,001$). Los métodos de medición mencionados anteriormente se utilizaron en siete mujeres con indicaciones de paracentesis antes y 30 minutos después del procedimiento. La reducción de la PIA después de este procedimiento fue mayor entre los pacientes con SHO crítico. Estos resultados están en consonancia con los cambios observados en el IAs tras la paracentesis.

Se observaron diferencias significativas entre los grupos en cuanto a las medidas de DAP ($p < 0,001$). Se encontró que la mediana de DAP del grupo de SHO leve (16 [RIC, 15-19]) era significativamente más baja que la del grupo de SHO grave

(24 [RIC, 23-27], p < 0,001) y crítica (26 [RIC, 24-28], p = 0,001). Además, la mediana de la DPA del grupo de SHO moderado (19 [RIC, 17-24]) fue significativamente menor que la del grupo de SHO grave (p < 0,005) y crítica (p < 0,05). Como era de esperar, DAP/TS aumentó progresivamente y tendió a ser el más alto en la etapa más sintomática de SHO (p < 0,001). La mediana de DAP/TS fue significativamente menor en pacientes con SHO leve (0,55 [RIC, 0,44–0,64]) en comparación con SHO grave (0,87 [RIC, 0,80–0,93]; p < 0,001) o SHO crítico (1,04 [RIC, 1,04 –1,13]; p < 0,001). De manera similar, la mediana de DAP/TS del grupo de SHO moderado (0,65 [RIC, 0,61–0,70]) fue significativamente más baja que la del grupo de SHO grave (p < 0,001) y crítica (p = 0,001). Como se anticipó, hubo una fuerte correlación positiva entre DAP/TS y PIA (r de Spearman = 0,886, p < 0,01). Además de eso, DAP/TS mostró una correlación positiva significativa con IAs (r de Spearman = 0,695, p < 0,01) y VO (r de Spearman = 0,622, p < 0,01).

Conclusiones

El presente estudio apoya la hipótesis del papel negativo de la HIA en el desarrollo de formas graves de SHO y sus complicados resultados.

El SHO se puede considerar como un modelo clásico del síndrome de HIA, donde la PIA es un importante marcador de diagnóstico asociado con la gravedad del SHO.

El SHO moderado se asoció con HIA grado I y el SHO grave con HIA grado II-III según la clasificación WSACS. En SHO crítico, el nivel de HIA corresponde a SCA.

Los indicadores de VO están relacionados con la gravedad del SHO y el nivel de HIA y son de particular importancia en la inicialización del SHO.

AsI es simple y conveniente para evaluar el grado de ascitis y puede servir como un indicador indirecto del volumen de reserva de la cavidad abdominal. Junto con los datos clínicos y de laboratorio, el índice de ascitis y los valores de PIA pueden ser indicadores de paracentesis.

La relación DAP/TS y su dinámica son marcadores importantes de la gravedad del SHO. La relación DAP/TS aumenta progresivamente, alcanzando los valores más altos en la etapa más sintomática del SHO y mostró la correlación positiva más fuerte con la PIA.

El monitoreo de DAP/TS puede ser un método de control indirecto de la reserva de PIA, Cab e VIA, y una herramienta adicional para la indicación de paracentesis.

La intervención temprana con culdocentesis o paracentesis previene la progresión del SHO y evita alcanzar PIAs críticas y las complicaciones asociadas.

La inclusión de la monitorización de la PIA en el estándar para el manejo del SHO podría ser útil para especificar la gravedad y el inicio oportuno del tratamiento, incluidos los métodos para reducir la PIA, prevenir una mayor disfunción orgánica y evitar la transición a una etapa más grave de la HIA y el SCA.

INTRODUCTION

Infertility affects 48.5–186 million people worldwide [1,2]. While the overall rates of infertility have remained approximately the same over the last 20 years, the use of assisted reproductive technology (ART) has increased [3,4]. Although ART is considered safe, women are at risk for developing ovarian hyperstimulation syndrome (OHSS), an important complication with significant morbidity and mortality [5-8].

OHSS is an iatrogenic complication caused by an excessive response to controlled ovarian stimulation. Exposure of ovaries to human chorionic gonadotrophin (hCG) or luteinizing hormone (LH) following controlled ovarian stimulation by follicle-stimulating hormone (FSH) underlies most cases of OHSS. [9-11]. As there is no consensus definition, the total number of OHSS cases is difficult to determine. However, within the literature, moderate to severe OHSS complicates 3–10% of all ART cycles, with an incidence of up to 20% in high risk women [12-14].

Ovarian hyperstimulation syndrome pathophysiology

The pathophysiology of OHSS relates to arteriolar vasodilation and increased capillary permeability resulting in intravascular volume shifting to the extravascular space [5,15,16]. Ovarian stimulation causes marked ovarian enlargement associated with an overproduction of pro-inflammatory and vasoactive cytokines leading to increased capillary permeability [14,17,18]. The use of hCG as an ovulatory trigger is associated with the development of OHSS, as hCG directly increases vascular endothelial growth factor (VEGF) production [10,19]. VEGF causes angiogenesis and increased vascular permeability. Similarly, the severity of OHSS has been directly linked to levels of VEGF [12,20]. Elevated levels of pro-inflammatory immune cytokines (i.e., interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor α (TNF-α) are characteristic of OHSS and are associated with increased capillary permeability [21]. Clinical manifestations of OHSS can be connected to the increased vascular permeability and subsequent loss of protein-rich fluid to the extravascular space [22].

Risk factors associated with the development of OHSS

•Young age (<35 years)

•Low body mass index – asthenic habitus

•Polycystic ovary syndrome (PCOS)

•History of atopy or allergies

•Previous episode of OHSS

•Pregnancy

•Higher or repeated doses of exogenous hCG

•Gonadotropin-releasing hormone (GnRH) – agonist protocol

•Use of Clomiphene citrate

•Increased number of developing follicles (>35)

•≥ 14 oocytes retrieved

•Elevated serum estradiol (>2500 pg/mL)

OHSS classification

Numerous attempts have been made to categorize and classify OHSS. Two forms have been described based on timing of presentation: an early form that typically occurs 3–7 days after ovulation triggering by hCG, and a late form occurring 12-17 days after hCG administration [23,24]. Early OHSS is caused by an excessive ovarian response to exogenous hCG, while late OHSS is due to excessive amounts of endogenous hCG from an implanting pregnancy of the Royal College of Obstetricians and Gynaecologists (RCOG) has classified OHSS into 4 stages based on clinical and laboratory features [25] (Table 1).

Table 1. ***RCOG classification of severity of OHSS***

Category	**Features**
Mild OHSS	Abdominal bloating Mild abdominal pain Ovarian size usually < 8 cm
Moderate OHSS	Moderate abdominal pain Nausea ± vomiting Ultrasound evidence of ascites Ovarian size usually 8-12 cm
Severe OHSS	Clinical ascites (± hydrothorax) Oliguria (<300 ml/day or < 30 ml/hour) Haematocrit > 0.45 Hyponatraemia (sodium < 135 mmol/l) Hypo-osmolality (osmolality < 282 mOsm/kg) Hyperkalaemia (potassium> 5 mmol/l) Hypoproteinaemia (serum albumin < 35 g/l) Ovarian size usually > 12 cm
Critical OHSS	Tense ascites/large hydrothorax Haematocrit > 0.55 White cell count > 25 000/ml Oliguria/anuria Thromboembolism Acute respiratory distress syndrome

Clinical presentation

The signs and symptoms of OHSS are a result of marked vascular permeability and concomitant uterine and ovarian enlargement [26]. Initial symptoms develop gradually with abdominal distention and mild abdominal discomfort due to reproductive organ enlargement with cysts [27,28]. These cystic ovaries may enlarge as much as 12-25 cm in some cases and have the potential to rupture or hemorrhage, leading to peritonitis. Similarly, these patients are at increased risk of ovarian torsion [16]. Increased capillary permeability leads to third spacing and subsequent

intravascular volume depletion. This pathophysiology underlies associated clinical features and severity as it correlates to increasing organ system involvement [29].

The first indication of OHSS is typically the development of ascites. Accumulation of ascitic fluid in the peritoneal cavity leads to abdominal distention and pain, as well as increased intra-abdominal pressure (IAP) [30]. Increased IAP may result in end-organ dysfunction, affecting the renal, respiratory, gastrointestinal, cardiovascular, and hepatic systems [31].

Further increases in IAP impairs splanchnicand hepatic perfusion resulting in local tissue hypoxia. Oliguria is one of the initial signs of intra-abdominal hypertension [32,33]. Intra-abdominal venous drainage is impaired, causing renal, intestinal, and hepatic edema. This leads to hepatic injury, paralytic ileus, and intestinal edema characterized by severe emesis and diarrhea [34].

Acute renal failure is typically characterized by hyponatremia due to a low serum osmolality and decreased urinary sodium excretion. Hyponatremia may lead to cerebral edema, altered mental status, and neurologic complications. Other metabolic abnormalities, including hyperkalemia and metabolic acidosis, may occur. Leukocytosis, increased hematocrit, and thrombocytosis indicate hemoconcentration and inflammation [35,36]. Hemoconcentration predisposes to hypercoagulability and thrombotic events, complicating up to 10 % of severe OHSS [37].

Critical patients may present with any combination of hypovolemic shock due to gastrointestinal losses or third spacing, septic shock due to an underlying infection, distributive shock from a severe inflammatory state, or obstructive shock secondary to pericardial effusion with cardiac tamponade or massive pulmonary embolism [5,38].

Definition and causes of intra-abdominal hypertension/abdominal compartment syndrome

Although initially recognized over 150 years ago, the pathophysiologic implications of IAP elevated have essentially been rediscovered only within the past two decades [39-41]. An explosion of scientific investigation and accumulation of clinical experience has confirmed the significant detrimental impact of both "intra-abdominal hypertension" (IAH), the presence of elevated intra-abdominal pressure, and "abdominal compartment syndrome" (ACS), the development of IAH-induced organ-dysfunction and failure, among the critically ill [42-44].

IAH has been identified as a continuum of pathophysiologic changes beginning with regional blood flow disturbances and culminating in frank end-organ failure and the development of ACS. ACS has been identified to be a cause of significant morbidity and mortality among critically ill surgical, medical, and pediatric patients [44-46]. Previously present, but significantly under-appreciated, IAH and ACS are now recognized as common occurrences in the intensive care unit (ICU) setting [47]. Elevated IAP has been identified as an independent predictor of mortality during critical illness and likely plays a major role in the development of multiple system organ failure, a syndrome which has plagued ICU patients and physicians for decades [33].

The most commonly used definition of ACS was published by the World Society on Abdominal Compartment Syndrome (WSACS) in 2013 [42]. This consensus document addresses clinical definitions and pressure measurement guidelines intended to assist clinicians and researchers in the diagnosis, treatment, and characterization of IAH/ACS. IAP is defined as the end-expiratory abdominal pressure in the supine position in the setting of fully relaxed abdominal wall musculature.

Measured IAP is used to calculate the abdominal perfusion pressure (APP) by subtracting IAP from the systemic mean arterial pressure; in this sense, APP can be

thought of as the abdominal analog to cerebral perfusion pressure and can be used as a predictor of visceral perfusion. The WSACS statement defines IAH as a sustained IAP greater than 12 mmHg, in contrast with normal IAP, which ranges from 2 to 7 mmHg. IAH is further subdivided into grades I to IV.

Consensus definitions as proposed by the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome.

- IAP is the steady-state pressure concealed within the abdominal cavity;
- IAP should be expressed in mmHg and measured at end-expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the mid-axillary line;
- The reference standard for intermittent IAP measurement is via the bladder with a maximal instillation volume of 25 mL of sterile saline;
- Normal IAP is approximately 5–7 mmHg in critically ill adults;
- IAH is defined by a sustained or repeated pathologic elevation of IAP ≥ 12 mmHg.

IAH is graded as follows:

• Grade I: IAP 12–15 mmHg

• Grade II: IAP 16–20 mmHg

• Grade III: IAP 21–25 mmHg

• Grade IV: IAP > 25 mmHg

ACS is defined as a sustained IAP > 20 mmHg (with or without an APP < 60 mmHg) that is associated with new organ dysfunction/failure.

Primary ACS is a condition associated with injury or disease in the abdomino-pelvic region that frequently requires early surgical or interventional radiological intervention. Secondary ACS refers to conditions that do not originate from the abdomino-pelvic region. Recurrent ACS refers to the condition in which ACS redevelops following previous surgical or medical treatment of primary or secondary ACS.

Intra-abdominal pressure (IAP)

The abdomen may be considered as a closed box with walls that are either rigid (costal arch, spine, and pelvis) or flexible (abdominal wall and diaphragm). The compliance of these walls and the volume of the organs contained within determine the pressure within the abdomen at any given time [48,49]. IAP is defined as the steady state pressure concealed within the abdominal cavity, increasing with inspiration (diaphragmatic contraction) and decreasing with expiration (diaphragmatic relaxation). IAP is directly affected by the volume of the solid organs or hollow viscera (which may be either empty or filled with air, liquid or fecal matter), the presence of ascites, blood or other space-occupying lesions (such as tumors or a gravid uterus), and the presence of conditions that limit expansion of the abdominal wall (such as burn eschars or third-space edema) [50-52]. While a variety of methods for IAP measurement have been described, intravesicular or "bladder" pressure has achieved the most widespread adoption worldwide due to its simplicity, minimal cost, and low risk of complications [53-55].

Abdominal compartment syndrome (ACS)

Among the majority of patients, critical IAP appears to be 10–15 mmHg. It is at this pressure that reductions in microcirculatory blood flow occur and the initial signs of organ dysfunction and failure are witnessed [56-58]. ACS is the natural progression of these pressure-induced end-organ changes and develops if IAH is not recognized and treated in a timely manner. Failure to recognize and appropriately treat ACS is commonly fatal while prevention and/or timely intervention is associated with marked improvements in organ function and patient survival [40,59,60]. In contrast to IAH, ACS is not graded, but rather considered an "all or nothing" phenomenon. The WSACS defines ACS as a sustained IAP > 20 mmHg (with or without an APP < 60 mmHg) that is associated with new organ dysfunction or failure [43; 61].

A comparison of pathophysiology and clinical picture indicates that symptoms of severe ovarian hyperstimulation syndrome and associated organ dysfunction are almost identical to intra-abdominal hypertension syndrome. A classic triad, including respiratory disorders, decrease in venous return, and restriction of internal perfusion is present in patients with severe ovarian hyperstimulation syndrome and intra-abdominal hypertension syndrome.

Article 1

The article titled ***«Ovarian hyperstimulation syndrome. A new look at an old problem»*** has been published in **Gynecological Endocrinology**.

The purpose of this article was to describe in practical items the clinical management of ovarian hyperstimulation syndrome based on modern aspects of its etiology and pathogenesis. The role of intra-abdominal hypertension in the development of the severe forms of ovarian hyperstimulation syndrome and its complicated outcomes was assessed.

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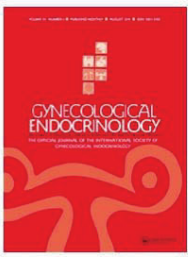
Ovarian hyperstimulation syndrome. A new look at an old problem.

Petrenko AP, Castelo-Branco C, Marshalov DV, Salov IA, Shifman EM.

Gynecological Endocrinology, the official journal of the International Society of Gynecological Endocrinology, covers all the experimental, clinical and therapeutic aspects of this ever more important discipline. It includes, amongst others, papers relating to the control and function of the different endocrine glands in females, the effects of reproductive events on the endocrine system, and the consequences of endocrine disorders on reproduction.

- Impact Factor (IF) **2.260 (2020)**
- 5 year Impact Factor **2.096 (2020)**
- It is located in the second quartile according Citescore (Scopus) and in the third quartile of the specialty of Obstetrics and Gynecology (position 54/83), according to the Journal Citation Reports 2020®.



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OVARIAN HYPER STIMULATION SYNDROME

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Ovarian hyperstimulation syndrome. A new look at an old problem

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ABSTRACT

To analyze the management of severe ovarian hyperstimulation syndrome based on aspects of its etiology and pathogenesis a systematic review of the literature was done. An evaluation of clinical trials, meta-analysis, case-reports and reviews assessing the management of different conditions related to ovarian hyperstimulation syndrome was made using the following data sources: MEDLINE Pubmed (from 1966 to July 2018) and the Cochrane Controlled Clinical Trials Register, Embase (up to July 2018). The role of intra-abdominal hypertension in the development of the severe forms of ovarian hyperstimulation syndrome and its complicated outcomes was assessed. The pathophysiology and clinic of intra-abdominal hypertension syndrome are almost identical to moderate and severe forms of ovarian hyperstimulation syndrome and associated organ dysfunction. The classic triad(respiratory disorders, reduction in venous return, and restriction of perfusion in internal organs) is present in severe ovarian hyperstimulation syndrome as well as in intra-abdominal hypertension syndrome. This review provides recommendations for the management of ovarian hyperstimulation syndrome and insight into the different medical complaints of this syndrome. The principles of therapy for intra-abdominal hypertension syndrome might be considered in the treatment of severe forms of ovarianhyperstimulation syndrome.

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Ovarian hyperstimulation syndrome; complications; intra-abdominal pressure; abdominal hypertension syndrome

Introduction

The inclusion of assisted reproductive technologies into routine clinical practice led to an increase in the number of pregnancies, the course of which may be associated with a wide range of complications. The main concerns are those related to ovarian hyperstimulation syndrome (OHSS) [1,2]. The syndrome was first time described in 1943 as 'syndrome d'hyperluteinisation massive des ovaries', and the first lethal outcome of OHSS due to renal failure was recorded in 1951, long before the first successful *in vitro* fertilization.

The frequency of OHSS varies widely – from 0.5% to 33% of all cycles of assisted reproductive technologies: Mild, moderate, and severe OHSS are diagnosed in 15–33%, 8–23% and 0.008–10% of patients respectively [1–3]. Although severe forms of OHSS are considered a rare complication in developed countries, the total number of this condition around the world is estimated in thousands with increasing frequency in recent years.

The development of a severe OHSS is associated with a high risk of death [4,5] being adult respiratory distress syndrome (ARDS), cerebral infarction, hepatic renal failure and pulmonary embolism the most frequent causes [6,7]. It is noteworthy that although mild forms of OHSS are considered as a common condition that usually resolves spontaneously, severe complications develop even with mild OHSS [4].

Treatment of severe forms of ovarian hyperstimulation syndrome should be considered from the perspective of multiple organ dysfunction syndrome; however, in the present clinical guidelines, intensive care units are referred only for giving symptomatic therapy. The actual strategy of treatment is to respond by rejection, not by foresight. The aim of the present review is to describe in practical items the clinical management of ovarian hyperstimulation syndrome based on modern aspects of its etiology and pathogenesis.

Material and methods

Systematic review: A systematic review of studies involving OHSS was carried out. To identify all of the articles assessing OHSS, the following search strategy was designed: '*ovarian hyperstimulation syndrome*' ([All Fields] and [MeSH Terms]) or '*intra-abdominal pressure*', ([All Fields] and [MeSH Terms]) or '*abdominal hypertension syndrome*'([All Fields] and [MeSH Terms] or 'Assisted reproductive techniques complications'[All Fields] and [MeSH Terms]) and ('humans'[MeSH Terms] and ('women'[MeSH Terms] or 'female'[MeSH Terms]) and 'adult'[MeSH Terms]). This strategy was adapted and applied to different Internet search engines to the MEDLINE database (1966–June 2018). There was no language, type of article or date restriction. This search was further supplemented by a hand-search of reference lists of selected review papers. 13,272 articles were screened, 1929 of them assessed for eligibility, and finally 30 were included in qualitative synthesis.

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Three reviewers (DVM, IAS, EMS) independently evaluated the eligibility of the manuscripts. Two reviewer (APP, CCB) extracted the data from the selected articles using a prefixed protocol (Information was gathered on the characteristics of the participants in the trial, the intervention and how the results were measured).

When extracting data from the selected reports, those that may be relevant for the pathophysiological management of OHSS were picked in a first screening. Afterwards, the most relevant were introduced in the present review. APP, DVM, IAS and EMS undertook the selection of the data and CCB checked any possible mistake occurred during the first extraction of data.

Of the articles reviewed, those that were not related to this specific syndrome, literature reviews not focused on the specific topic (OHSS with intraabdominal hypertension) or those whose purpose was not to demonstrate a therapeutic impact or management of OHSS in adult life were not considered. In the final selection of articles only those using diagnostic techniques, treatments or medical procedures that are currently recognized were taken into account.

Results

Pathogenesis of ovarian hyperstimulation syndrome

The pathogenesis of OHSS is complex and many of its aspects have not yet been elucidated. Currently, OHSS is considered as a systemic aseptic inflammatory response of the vascular endothelium to abnormally high plasma concentrations of sex steroids, accompanied by generalized endothelial damage and pronounced vascular permeability. The core of the pathogenesis of OHSS is the boost of systemic regulatory biologically active substances disproportionately produced by ovaries in cases of increased receptor sensitivity to the stimulating effect of follicle-stimulating hormone (FSH), and/or human chorionic gonadotropin (hCG) [1,4] (Figure 1). The syndrome is based on the phenomenon of 'increased vascular permeability', leading to a massive yield of protein-rich fluid into the 'third space', interstitium and the formation of ascites, hydrothorax and anasarca [1,2]. However, an unknown factor leading to fluid transudation remains unsettled. Leading links in the launching of pathophysiological cascades of the OHSS are the role of vascular endothelial growth factor (VEGF) in a context of VEGF receptors' imbalance and the activation of the renin-angiotensin system. High concentrations of interleukins (IL-1, IL-2, IL-6, IL-8), tumor necrosis factors (TNF-α, TNF-β) were detected in patients with OHSS in blood plasma, follicular fluid and peritoneal transudate [8].

The consequences of this pathological process are hypovolemia and hemoconcentration, large protein losses, thromboembolic complications, the formation of polyserosites, impaired renal perfusion, oliguria, abnormal liver function, the development of intra-abdominal hypertension, the development of acute respiratory failure, and in severe cases the development of multiple organ failure [1,4,9].

The role of intraabdominal hypertension

Data suggest that intense ascites with intra-abdominal hypertension (IAH) is a main factor for unfavorable outcomes in OHSS patients [10,11]. Many medical conditions are related to intra-abdominal hypertension syndrome [12,13] i.e. abdominal compartment syndrome (ACS) may have its origin in an increase in intra-abdominal pressure (IAP) secondary to severe ascites [13,14]. Increased abdominal pressure may compromise organ perfusion, which is a potentially life-threatening condition [12]. However, in spite of this concern, data on IAP indices in patients with OHSS are reflected in only six publications [15,9,16–19] (Table 1).

In four of these reports, IAP had a wide range of values from I to IV IAH grade [15–17,19]. It is to note the report by Cil et al. who described a case of OHSS in which measurement of IAP was done in two placements: transgastric and transvesical [15]. The patient had a pronounced adhesion process in the lower abdomen and therefore the measurement of IAP by alternative methods gave different results: Transvesical IAP was 54 cmH_2O (40 mmHg) corresponding to IAH grade IV whereas when IAP was measured through the stomach raised only up to 20 cmH_2O (14.8 mm Hg), which corresponded to IAH grade I.

In a clinical trial assessing the relationship of IAP with intra-abdominal volume (volume of ascites, size of the ovaries) and compliance of the anterior abdominal wall in 60 women with different degrees of OHSS, the mean value of IAP did not reach levels of IAH in the cases of mild OHSS, while moderate OHSS was associated to IAH grade I, and severe to II–III IAH grade. The most important finding in this study was that the volume of the ovaries and ascites were important factors in the initialization of the IAP increase, but the compliance of the anterior abdominal wall was the determining factor in the progression of IAH in patients with OHSS [18]. Therefore, although evidence suggests the role of IAH in OHSS, research on this topic is of a single nature and many questions remain undisclosed.

The debut of the clinical picture of OHSS is gastrointestinal symptomatology [1,2,20]. Nausea, diarrhea, and bloating are present in almost 100% of cases. Biochemical markers of hepatic

Table 1. Reports on intra-abdominal pressure indices in patients with ovarian hyperstimulation syndrome.

Author	n	OHSS stage	IAP mmHg	IAH grade	Outcomes	Type of study
Cil T. et al. [15]	1	Severe	Stomach 14,8 Bladder 40	I IV	IAP measurement	Clinical case
Maslovitz S. et al. [9]	19	Moderate and Severe	12,9 ± 0,91	I	effect of paracentesis on IAP and renal blood flow	Clinical trial
Lobo C., Twigg S. [16]	1	Severe	14–19	II		Clinical case
Marak C. et al. [17]	1	Severe	28	IV		Clinical case
Marshalov D. et al. [18]	60	Mild Moderate Severe	7,05 ± 1,76 13,65 ± 1,92 20,60 ± 2,52	- I II-III	Relationship between IAP, intra-abdominal volume (volume of ascitic fluid, size of the ovaries) and compliance of the anterior abdominal wall	Clinical trial
Makino H. et al. [19]	1	Severe	25	IV	Intravesical pressure measurement in the management of OHSS.	Clinical case

Values of IAP and IAH grade are given in accordance with the international recommendations of the WSACS (World Society of the Abdominal Compartment Syndrome) in mmHg, where Grade I – 12–15 mmHg; II – 16–20 mmHg; III – 21–25 mmHg; IV > 25 mmHg.

dysfunction are observed in 25–45% of cases [21]. Results of liver biopsy in patients with OHSS showed significant morphological abnormalities at the ultrastructural level. Cases of recurrent course of cholestasis during pregnancy up to the third trimester have been reported [6].

The process of IAH progression, regardless of the etiologic factor, also suggests the primary damage to the gastrointestinal tract. Compression of mesenteric veins leads to abdominal venous hypertension; mesenteric blood flow decreases; due to low perfusion pressure, intestinal ischemia develops; growing regional PCO_2, intragastric acidosis; increased interstitial edema and permeability, resulting in increased translocation of bacteria; the concentration of proinflammatory cytokines (IL-1b, IL-6, TNFa) is progressively increasing; often ulcer bleeding and necrotic enterocolitis; develops paralytic or mechanical ileus; peritoneal adhesion. As a result of the decrease in the splanchnic blood flow, port-collateral blood flow is disrupted occurring visceral edema of the liver, decreased glucose metabolism, lactate acidosis progression and concentration of toxic metabolites [22].

With increasing severity of OHSS, kidney function may be affected [23]. Pronounced hypovolemia and compression of the renal parenchyma by enlarged ovaries are the commonly attributed causes, however, a study by Maslovitz highlighted the relationship between the dynamics of the IAP in the OHSS and restrictions of renal blood flow, diuresis and nitrogen balance [9]. Other authors, after unsuccessful attempts to restore diuresis with replacement of blood volume and correction of oncotic plasma pressure, confirmed the role of mechanical compression of renal veins due to pronounced IAH and detected recovery of diuresis after decompression [19].

It is known that when the level of IAP exceeds 10–12 mm Hg. there is a compression of the kidney parenchyma resulting in a decrease of renal blood flow; tubular dysfunction; decrease in diuresis (oliguria and anuria); prerenal azotemia and the concentration of antidiuretic hormone, renin, angiotensin, aldosterone, which potentiates arterial vasoconstriction [22].

Further progression of OHSS is accompanied by respiratory disorders. Difficulty in breathing occurs in 92% of cases, but with the development of pleural effusion, it can be associated only in 21% of cases of OHSS [21]. Again, the origin lies in the pathophysiology of IAH: the contraction of the diaphragm leads to external compression of the pulmonary parenchyma and as a consequence the functional pulmonary volumes decrease significantly while the respiratory dead space increases; compression atelectasis develops; an intrapulmonary bypass increases, ventilation diffusion decreases; hypercapnia increases, oxygen transportation decreases; alveolar edema increases due to increased extravascular lung water, which increases the risk of ARDS development; activation of pulmonary neutrophils leads to inflammatory infiltration of the lungs and an increase in the incidence of pulmonary infectious complications [22].

With the growth of IAP, further cranial displacement of the diaphragm leads to cardiac compression; the pleural and intrathoracic pressure continues to increase; blood flow in the inferior vena cava decreases, venous return and preload occurs; the global end-diastolic volume of the heart and the global, right-left ventricular ejection fraction decrease; general peripheral vascular resistance, vascular resistance of the lungs, pressure in the pulmonary artery increase, which also adversely affects the balance of extravascular lung water; venous stasis increases the frequency of venous thrombosis and pulmonary thromboembolism. It is also to note that cardiovascular effects of IAH increase with hypovolemia and that in OHSS, a significant decrease in venous return, cardiac output, and increased vascular resistance have been described [5]. The most serious problem with OHSS is thrombotic complications, with severe forms of OHSS occurring in 10% of cases [7].

IAH adversely affects the central nervous system. High intrathoracic pressure complicates venous outflow along the internal jugular veins, which results in an increase in intracranial pressure and cerebrovascular resistance reducing cerebral perfusion pressure. This condition has been also described with OHSS [24].

IAH also disrupts uterine blood flow, which adversely affects pregnancy-bearing [25]. In the analysis of the dependence of unfavorable outcomes of pregnancy and the severity of IAH with OHSS, a strong positive correlation was found – $r = 0.726$, $p < .001$ [18].

Consequently, by comparing the symptoms and complications of intra-abdominal hypertension syndrome with the criteria used to classify the severity of OHSS, it can be stated that they are practically identical. Figure 2 summarizes the clinical effects of IAH in OHSS.

The relation between IAH and OHSS

Four groups of factors influence the development of IAH (Table 2): the first and second groups include conditions that increase the content of the abdominal cavity and accumulate pathological fluid or gas. Enlarged ovaries, ascites, intestinal ileus and intestinal pneumatosis clearly contributed to IAH development in cases of OHSS.

The relation of IAP with the volume of abdominal cavity is nonlinear. IAP increases disproportionately in response to equivalent rise in volume. The dynamics curve of IAP related to the increase in intra-abdominal volume was first described in patients with chronic peritoneal dialysis. Changes in fluid volumes during peritoneal dialysis are close to the described dynamics of increase in ascitic fluid volume in patients with OHSS [26]. The curve of IAP dynamics in patients with chronic dialysis had three phases. The initial phase corresponding to the onset of fluid administration is characterized by a moderate increase in the IAP. The middle phase lasted with an increase in the volume of liquid to 3 liters with minimal increase in IAP, but patients complaint with enlarged waist and abdominal discomfort. The last phase occurred when the injected volume exceeded 3 liters. In this phase, linear increase in IAP and marked discomfort in the abdomen and nausea occurs while the waist circumference increased already slightly. A linear relationship between IAP and enlargement (compliance) of the abdominal wall exists and, therefore, the extensibility of the anterior abdominal wall is a determining factor in the progression of IAH in patients with OHSS [18]. Compliance of the abdominal wall decreases as the content of the abdomen increases. Animal experimental models have demonstrated a decrease in compliance of the abdominal wall from 10.8 to 0.56 ml/mmHg/kg when IAP increased from 0 to 40 mmHg [27]. It is important to note that the intensity of growth of IAP in response to an increase in intra-abdominal volume directly depends on the initial compliance of the abdominal wall of the subject [22]. Thus, a more intensive increase in IAP will be observed in primordial, asthenic, women with scars on the anterior abdominal wall and adhesive process in the abdominal cavity. Young age and asthenic phenotype are risk factors for the development of severe form

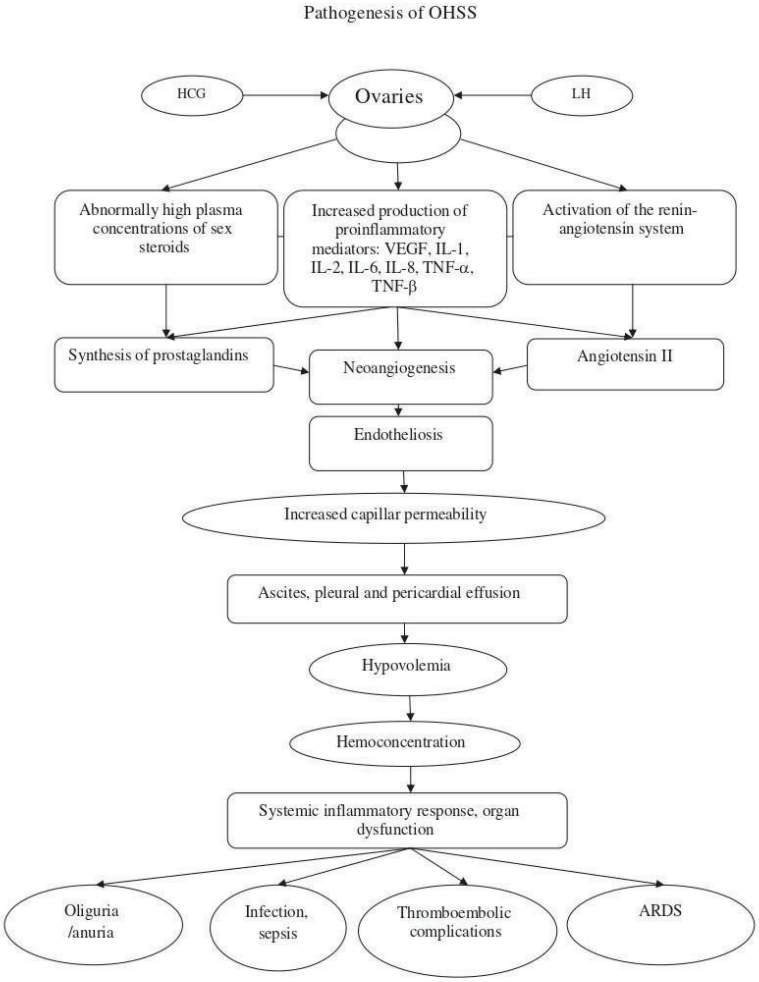

Figure 1. Pathogenesis of OHSS.

of OHSS [1,2]. In one of the above described clinical observations of severe OHSS, accompanied by a critical increase in IAP (up to 40 mmHg), the patient had a pronounced adhesive process in the abdominal cavity and scars in the anterior abdominal wall [15]. Consequently, the third group includes factors that contribute to reducing the extensibility of the anterior abdominal wall. Factors contributing to a decrease in the extensibility of the anterior abdominal wall and the accumulation of abnormal fluid in the abdominal cavity also include the 'capillary leak' syndrome inherent in OHSS. In turn, factors contributing to the progression of 'capillary leak' are allocated to a separate - the fourth group. These include: acidosis, coagulopathy, bacteremia, sepsis, aggressive infusion therapy and polytransfusion. In addition to the fact that all these factors are observed in the severe and critical form of OHSS, the pathogenesis of the OHSS itself is associated with increased vascular permeability.

Pathophysiologic treatment for OHSS

Additional evidence of the robustness of the concept of the pathogenetic role of IAH in the formation of adverse outcomes in OHSS is the effectiveness of abdominal decompression's data.

The beneficial physiological effects of paracentesis were documented in the treatment of massive ascites, including patients with OHSS [28]. It is well known that paracentesis in patients with cirrhosis led to a decrease in the IAP and an increase in the shock volume of the heart and subsequently to an increase in venous return and an improvement in the filling of the heart chambers. Thaler et al. were the first to describe the benefits of paracentesis in patients with OHSS and reported significant clinical improvement after ascitic fluid removal [29]. After this procedure, patients with OHSS significantly improve renal blood flow and increase diuresis as well as decrease the intensity of pulmonary symptoms and reduce the severity of respiratory

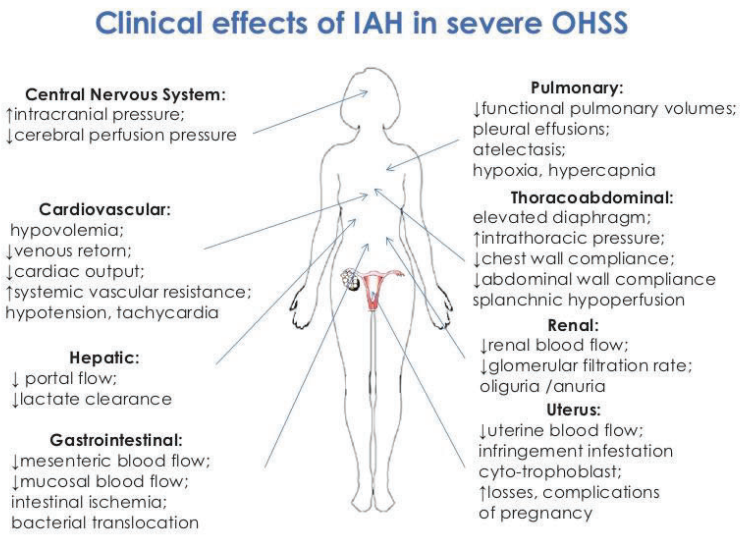

Figure 2. Clinical effects of IAH in severe OHSS.

Table 2. Risk factors for intra-abdominal hypertension in OHSS.

Factors that increase the content of the abdominal cavity	Factors that contribute to the accumulation of pathological fluid or gas	Factors that contribute to the abdominal wall compliance's decrease	Factors that contribute to the progression of the «capillary leak»
• Enlarged ovaries • Ascites • Hemoperitoneum • Gastroparesis • Intestinal ileus	• Activation of the ovaries' production of the vasoactive mediators on the background of stimulation of superovulation • Loss of fluid into the third space: ascites, pleural and pericardial effusions • A delayed evacuation of gastric and intestinal contents, constipation, flatulence	• Young age • Asthenic physique • First pregnancy • The presence of cicatricial changes of the anterior abdominal wall and the adhesive process in the abdominal cavity • Abdominal wall tension due to the pain • Edema of the retroperitoneal space	• Increased production of proinflammatory mediators: VEGF, IL-1, IL-2, IL-6, IL-8, TNF-α, TNF-β • Abnormally high plasma concentrations of sex steroids • Endotheliosis • Acidosis • Coagulopathy • Hypothermia • Hypoproteinemia • Polytransfusion, • massive fluid resuscitation or positive fluid balance • Bacteremia • Infectious complications-sepsis

failure [30]. After evacuation of ascites in patients with OHSS, a decrease in hematocrit and leukocytosis is also observed [30]. Moreover, after paracentesis pregnant women showed an increase in uterine perfusion [26]. The positive dynamics after paracentesis in patients with OHSS, might be explained by the effect of the decrease in the IAP due to the removal of the fluid. However, in most cases, a statistically significant decrease in IAP is only recorded when at least 2000 ml of the liquid was removed. Controversially, improvement in renal blood flow and urinary function occurred with the removal of much smaller volumes of fluid [9]. This result suggests that the effect of paracentesis depend not on the volume of the removed liquid, but on decompression as such.

One of the goals of OHSS treatment is to prevent the progression of the severity of the syndrome. The previously recommended criteria for paracentesis were complaints of shortness of breath, abdominal distention, abdominal pain, oliguria, and ineffective treatment. In its first edition, the «Management of ovarian hyperstimulation syndrome, Green-top guideline, № 5» recommended paracentesis when the increase in IAP higher than 20 mmHg (Level of Recommendations III) [23]. However, whether the OHSS is considered from the point of view of the IAH syndrome, then early decompression, even with a moderate form of OHSS when ascites is not expressed, may be probably justified. In recent years, a reassessment of the importance of IAH in the OHSS is in motion. In the «Ovarian Hyperstimulation Syndrome (OHSS). Diagnosis and Management. Guideline № 9» [20], a recommendation on early decompression is performed, even in an outpatient basis (Level of Recommendations 2B-II). Moreover, it has been proved that culdocentesis avoid the progression of OHSS to severe forms [20]. In the latest edition of the guideline «The management of the ovarian hyperstimulation syndrome, Green-top guideline, № 5» (2016), the specific values of IAP (20 mmHg), in which it is necessary to proceed to paracentesis, have been replaced by an abstract 'increase' in IAP, which indicates the possibility of development of organ

dysfunction with lower values of IAP [4]. Obviously, there is insufficient clinical data to establish the critical values of IAP in patients with OHSS.

Conclusions

This systematic review and analysis of literature supports the hypothesis of the potential role of intra-abdominal hypertension in the development of severe forms of ovarian hyperstimulation syndrome and its complicated outcomes. A comparison of pathophysiology and clinical picture indicates that symptoms of severe ovarian hyperstimulation syndrome and associated organ dysfunction are almost identical to intra-abdominal hypertension syndrome. A classic triad, including respiratory disorders, decrease in venous return, and restriction of internal perfusion is present in patients with severe ovarian hyperstimulation syndrome and intra-abdominal hypertension syndrome.

Therefore, the therapeutic principles for ovarian hyperstimulation syndrome should be consistent with the principles of therapy for intra-abdominal hypertension syndrome. The question of intra-abdominal hypertension and its effect on the course and outcomes of ovarian hyperstimulation syndrome remains insufficiently clarified, which stimulates further research in this field.

Disclosure statement

The authors declare no conflict of interest.

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Disposition

Mild to moderate OHSS may be managed on an outpatient basis, while severe OHSS requires inpatient management [62]. Early consultation with the obstetrics and gynecology team, as well as any subspecialties, is recommended. Patients presenting with severe abdominal pain or distention, intractable emesis, hemoconcentration, abnormal liver function studies, IAH/ACS, oliguria or anuria, hypotension, tachypnea, dyspnea, syncope, and/or electrolyte disturbances such as hyponatremia or hyperkalemia should be hospitalized [9].

Management

The treatment of OHSS is primarily supportive, and in most cases, OHSS follows a self-limited course that parallels the decline in serum b-hCG [63]. Mild and moderate OHSS may be treated on an outpatient basis with symptomatic relief, monitoring, and close follow up in 2-3 days [64]. These patients should be counseled about the need to monitor fluid intake (approximately 2 L water daily) and output, body weight, abdominal girth, and the necessity of avoiding nephrotoxic medications, including non-steroidal anti-inflammatories [62].

Thromboprophylaxis with pregnancy-related low-molecular weight heparin (LMWH) doses. Clinically, progression of thromboembolism is seen in approximately 10% of cases, and appropriate anticoagulation must be implemented promptly in the department [65]. Strict return precautions, including worsening symptoms, weight gain of 1 kg/day or more, and urine output < 500 mL/day should be provided [14]. The patient should be aware that her condition may worsen if pregnancy occurs.

For severe cases of OHSS, management is aimed towards maintaining circulatory hemodynamics, mobilizing fluid from the third space back into the vessels, correcting hemoconcentration, and respiratory support. Restoration of adequate intravascular volume must always remain the first priority to ensure appropriate tissue perfusion and prevent the development of multiorgan failure. Correction of

hypovolemia, hypotension, and decreased renal perfusion takes precedence, accepting that fluid administration may contribute to the accumulation of ascites [66]. Either normal saline or a balanced crystalloid solution is the initial resuscitation fluid of choice [67]. However, albumin can be used to expand plasma volume in the presence of severe hemoconcentration (hematocrit 45%), severe hypoalbuminemia (serum albumin level ≤ 3.0 g/dL), or significant ascites with elevated IAP [68].

Other volume expansion agents including fresh frozen plasma, hydroxyethyl starch (HES), and dextran have been used with limited success in OHSS, but are not recommended as first-line agents [14]. Intravascular resuscitation should be titrated to maintain an adequate urine output (N20–30 mL/h) and to reverse hemoconcentration. The addition of vasopressor therapy may be needed to maintain adequate perfusion. While there is little empiric data to guide management, the underlying pathophysiology of OHSS favors norepinephrine and dopamine as potential options [64]. Dopaminergic agonists, including cabergoline, have been established as effective therapies for the prevention of OHSS via blockage of VEGF expression [9]. Published data suggests that dopamine itself improves the clinical evolution of established OHSS, although no randomized controlled trials have been published to confirm its effectiveness [14].

Correction of severe electrolyte abnormalities plays an important role in OHSS management. Hyperkalemia in these patients should be managed in the usual fashion [69]. Salt or water restriction is not recommended, as this does not affect the patient's weight, peripheral edema, intravascular volume status, or abdominal circumference [70]. Current evidence suggests that hypertonic saline solutions, either alone or in combination with colloid solutions, result in significant reduction in IAP while expanding intravascular volume and correcting hyponatremia present in OHSS. Hypertonic saline (3%) may be considered as a 100–150 mL infusion over 5-10 min with a repeat bolus as needed in those with severe OHSS. The goal for serum sodium correction should be 1-3 mEq/L in the first hour [71].

Pulmonary support may involve thoracentesis, oxygen supplementation, non-invasive ventilation, or mechanical ventilation [72,73]. If acute respiratory distress syndrome (ARDS) develops, mechanical ventilation using 6 mL/kg of predicted body weight and plateau pressure < 30 cm H2O should be initiated [74]. The presence of ARDS presents a fluid management challenge, however, fluid therapy should be titrated to maintain systemic perfusion and adequate renal perfusion [12]. Diuretics may potentiate hemoconcentration and hypovolemia, predisposing the patient to venous thromboembolism, and should also be avoided if at all possible [75]. Glucocorticoids may provide some benefit in the treatment of ARDS in the setting of OHSS, with case reports reporting favorable outcomes with 30 mg/kg methylprednisolone [76].

While ascites is a hallmark feature of OHSS, paracentesis is not indicated in every OHSS patient. Indications for paracentesis include symptomatic complaints such as dyspnea, abdominal distention, and oliguria. Additional indications include evaluation for spontaneous bacterial peritonitis and the presence of IAH/ACS [77]. Serial IAP measurements and urine output should be obtained via a urinary catheter [42]. Based on current guidelines for the management of IAH and ACS, an IAP N20 mmHg warrants peritoneal decompression through paracentesis [42]. While there is no required volume of peritoneal fluid to be removed, 1000 mL is an appropriate initial amount. The average amount of peritoneal fluid drained during hospitalization is approximately 11 L [70]. However, there are reported cases of patients requiring up to 7.5 L on one occasion and 45 L in total during 1 hospitalization [78]. Large volume paracentesis may lead to rapid re-accumulation of ascites, removing proteins from the intravascular compartment, thereby worsening third spacing [79]. Ultrasound guidance should be utilized in order to avoid puncturing large ovarian cysts, with albumin infused as necessary to maintain intravascular volume [9].

Surgical management for OHSS is indicated in the presence of ovarian torsion, pregnancy termination, intra-abdominal hemorrhage, ectopic/heterotopic

pregnancy, or ruptured cysts. When infection is suspected, empiric antibiotic therapy should be initiated [25].

For the standpoint of intensivists, OHSS is a multiple organ dysfunction syndrome; however, in the present clinical guidelines, intensive care units are referred only for giving symptomatic therapy. Nowadays, the actual strategy is to act against symptom, not by foresight. Infusion therapy begins when life-threatening hemoconcentration appears, paracentesis is performed in case of oliguria, which may develop anuria, respiratory failure, arterial hypotension, and multiple organ failure. It is noteworthy that new data on intensive therapy for OHSS in the latest Green-top guideline No.5 by the RCOG have not been recorded over the last decade [25]. Recent published manuscripts highlight the fact that intense ascites and the accompanying IAH are the main factors for adverse outcomes in OHSS [15,35,80] and based on pathophysiologic data our group was able to establish an analogy between OHSS and IAH syndrome [18]. Furthermore, as the pathophysiology and clinical picture of severe OHSS and its associated organ dysfunction are almost identical to IAH syndrome or ACS, the management of OHSS may be considered also from the perspective of an IAH condition.

Article 2

The article titled ***«Perspective Advices in the Management of Ovarian Hyperstimulation Syndrome»*** has been published in **Journal of Gynecology and Women's Health.**

Mini Review presenting perspective advices in the management of Ovarian Hyperstimulation Syndrome

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Perspective Advices in the Management of Ovarian Hyperstimulation Syndrome

Aleksei Petrovich Petrenko and Camil Andreu Castelo Branco Flores

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Perspective Advices in the Management of Ovarian Hyperstimulation Syndrome

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Abbreviatation: OHSS: Ovarian Hyperstimulation Syndrome; IAH: Intra-Abdominal Hypertension Syndrome; ACS: Abdominal Compartment Syndrome; IAP: Intra-Abdominal Pressure

Mini Review

The increasing availability around the world of in vitro fertilization helps many patients who would be otherwise unable to conceive; however, this procedure has also some disadvantages. Among them, the increased risk of ovarian hyperstimulation syndrome (OHSS) mainly related to the use of human chorionic gonadotropin in assisted reproduction. As the pathophysiology and clinical picture of severe OHSS and its associated organ dysfunction are almost identical to intra-abdominal hypertension syndrome (IAH) or abdominal compartment syndrome (ACS), the management of OHSS may be considered also from the perspective of an IAH condition [1,2]. The classic triad, including respiratory disorders, decrease in venous return, and restriction of internal perfusion is present both in severe OHSS and IAH patients. Several studies related specific indices of the intra-abdominal pressure (IAP) with varying degrees of OHSS [3-7]. According to these data, the condition of IAH Grade I in moderate OHSS and IAH Grade II-III in severe OHSS are present [8]. Therefore, if we accept the hypothesis that both syndromes are similar, then the principles of OHSS therapy should be consistent with those drawn on the treatment of IAH.

The typical picture of severe OHSS is a young asthenic woman in her first pregnancy with a tense, enlarged abdomen, often with postoperative scars on the anterior abdominal wall. In this description, several risk factors that reduce compliance of the abdominal wall (Cab) are recorded. The abdominal cavity, with its unique anatomy and physiology, has a sophisticated sensitivity to pressure and perfusion being the role of Cab one of the most important. While preserving the reserve of extensibility of the anterior abdominal wall intra-abdominal pressure (IAP) grows slowly, but when this reserve is consumed IAP grows exponentially with a characteristic clinic of internal organ perfusion disorders, including respiratory, renal-hepatic and, ultimately, multiple organ failure.

Surgical decompression is presently an alternative used in the treatment of severe OHSS. Some authors describe a significant improvement of the renal blood flow and an increase of the diuresis after paracentesis or culdocentesis [9-11]. This positive trend can be explained by the effect of a decrease in IAP secondary to fluid removal. However, in most cases, a significant decrease in IAP is only recorded after 2000 or more ml of ascites removal. Controversially, an improvement in renal blood flow and urinary function occurred with the removal of much lesser volumes of fluid [12]. These data suggest that the effect of paracentesis depend not on the volume of fluid removed, but rather on the effect of decompression itself. Nevertheless, currently criteria for performing paracentesis are complaints of shortness of breath, abdominal distension, abdominal pain, oliguria, and treatment failure, i.e. already developed multiple organ dysfunction. If OHSS is considered from the perspective of IAH syndrome, then early decompression, even in patients with a moderate form of OHSS, when ascites is not expressed, may be probably justified.

The procedure of negative extra-abdominal pressure (NEXAP) is one of the future promising options for non-invasive treatment of IAH/ACS [13,14]. Scientific studies on the physiological effects of localized decompression began in 1959 with a method for abdominal decompression anticipated by Heyns OS [15]. The device was a sealed chamber superimposed on the patient's abdomen and a vacuum pump for the local depositing. Noteworthily, the history of abdominal decompression is a typical example in the history of medical innovations: the description of the phenomena, its silencing, the rediscovery of the previously described phenomena, skepticism in relation to already known facts and its subsequent acceptance. The initial studies were carried out decades ago before the standard use of Doppler ultrasound as a diagnostic tool; consequently, the practical implementation of such method was ahead of the development of its theoretical justification.

Only two studies on abdominal decompression are recorded in the Cochrane Database. One of them states that there is no benefit from the prophylactic use of abdominal decompression in healthy pregnancies [16]. On the contrary, in the second one including pregnant women having preeclampsia a positive therapeutic effect was demonstrated [17]. Several studies have shown the effectiveness of NEXAP in reducing not only IAP, but also intracranial and pleural pressure with subsequent improvement of lung volumes and chest elasticity [18-20]. NEXAP is simple and easy to apply to the patient, but the common drawback for the NEXAP devices is the occasional incompatibility between the dimensions of the chamber and patient's anatomy.

A modern equipment for abdominal decompression (KAD-01-ACS known as "The hope") have been developed in St. Petersburg (Russia) to avoid these drawbacks. The experience using this equipment showed the high efficiency of NEXAP in the treatment of different women's reproductive health conditions [21-25]. Considering OHSS as a polycompartmental syndrome, NEXAP may be used in its treatment as early as possible to prevent further organ dysfunction and to avoid the transition to a severe stage of IAH and ACS. NEXAP is a promising option in the pathogenetic treatment of IAH, but so far it has not been used in the treatment of OHSS. In spite of the benefits showed in the initial studies, there are a large number of emerging questions that embrace the safety of NEXAP methods, the need to implement continuous monitoring of IAP, the difficulty in measuring or calculating Cab, the possible discrepancy between the IAP markers and the real IAP; the severity of OHSS at which NEXAP should be indicated, the question of the negative pressure and others related to the procedure itself as how is the best NEXAP scheme (intermittent, continuous, how many times a day,...) and how long the effect of the procedures will last. All these issues are grounds for future research in this area.

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Article 3

The article titled ***«Alternative strategies for the management of ovarian hyperstimulation syndrome, the role of intra-abdominal hypertension control»*** has been published in **Gynecological Endocrinology.**

The purpose of this article was to analyze the methods for reducing intra-abdominal pressure in the management of the moderate and severe forms of ovarian hyperstimulation syndrome. This review provides suggestions for the OHSS management of based on the principles of therapy for intra-abdominal hypertension syndrome.

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Alternative strategies for the management of ovarian hyperstimulation syndrome, the role of intra-abdominal hypertension control

Petrenko AP, Castelo Branco C, Marshalov DV, Salov IA, Kuligin AV, Shifman EM, Chauke SS.

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Alternative strategies for the management of ovarian hyperstimulation syndrome, the role of intra-abdominal hypertension control

Aleksei Petrovich Petrenko, Camil Castelo Branco, Dimitry Vasilevich Marshalov, Igor Arkadevich Salov, Alexander Valerievich Kuligin, Efim Munevich Shifman & Shane Shitsundzuxo Chauke

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REVIEW

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Alternative strategies for the management of ovarian hyperstimulation syndrome, the role of intra-abdominal hypertension control

Aleksei Petrovich Petrenko[a,b,c], Camil Castelo Branco[a], Dimitry Vasilevich Marshalov[b,c], Igor Arkadevich Salov[d,c], Alexander Valerievich Kuligin[b], Efim Munevich Shifman[e] and Shane Shitsundzuxo Chauke[f,g]

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ABSTRACT

The aim of this study is to analyze the methods for reducing intra-abdominal pressure (IAP) in the management of the moderate and severe forms of ovarian hyperstimulation syndrome (OHSS). We carried out a systematic review of the literature. An evaluation of clinical trials, meta-analysis, case-reports, and reviews assessing the management of conditions associated with OHSS and intra-abdominal hypertension (IAH)/abdominal compartment syndrome (ACS) was made using the following data sources: MEDLINE Pubmed (from 1966 to July 2019) and the Cochrane Controlled Clinical Trials Register, Embase (up to July 2019). The principles of treatment of IAH syndrome can be considered in the treatment of moderate and severe forms of OHSS. Medical treatment of patients with increased IAP in OHSS should be started early to prevent further organ dysfunction and avoid a transition to a more severe stage of IAH and ACS. Some of the new, non-surgical methods, such as continuous negative extra-abdominal pressure, are a promising option in specific groups of patients with OHSS. This review provides suggestions for the management of OHSS based on the principles of therapy for IAH syndrome. Further well-designed studies are needed to confirm these initial data.

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Introduction

The increasing availability around the world of *in vitro* fertilization helps many patients who would be otherwise unable to conceive; however, this procedure has also some inconveniencies. Among them, the increased risk of ovarian hyperstimulation syndrome (OHSS) mainly related to the use of human chorionic gonadotropin in assisted reproduction [1,2]. As OHSS is the most important risk in ovarian stimulation procedures, every attempt should be made to identify patients at higher risk. Preferably, subjects at risk should be identified prior to stimulation, and stimulation protocols should be selected minimizing the risk of OHSS. Although the use of GnRH antagonist protocols with a GnRH agonist to trigger final oocyte maturation of oocytes is an effective approach for prevention [3], in some cases severe OHSS occurs.

The etiology of OHSS is often due to iatrogenic intervention, and the pathogenesis is a controversial topic. OHSS requires a background of abnormally high blood concentrations of sex steroid hormones, which negatively affect the functions of various body systems and cause systemic inflammatory response, coagulopathy and multiple organ failure [3–6]. Occasionally, the development of severe and critical forms of OHSS compels its management in intensive care units, where adequate monitoring and treatment of this condition is provided. For the standpoint of intensivists, OHSS is a multiple organ dysfunction syndrome; however, in the present clinical guidelines, intensive care units are referred only for giving symptomatic therapy. Nowadays, the actual strategy is to act against symptom, not by foresight. Infusion therapy begins when life-threatening hemoconcentration appears, paracentesis is performed in case of oliguria, which may develop anuria, respiratory failure, arterial hypotension, and multiple organ failure. It is noteworthy that new data on intensive therapy for OHSS in the latest *Green-top* guideline *No.5 by The Royal College of Obstetricians and Gynaecologists* have not been recorded over the last decade [7].

Recent published manuscripts highlight the fact that intense ascites and the accompanying intra-abdominal hypertension (IAH) are the main factors for adverse outcomes in OHSS [8–11] and based on pathophysiologic data our group was able to establish an analogy between OHSS and IAH syndrome [12]. Furthermore, as the pathophysiology and clinical picture of severe OHSS and its associated organ dysfunction are almost identical to IAH syndrome or abdominal compartment syndrome (ACS), the management of OHSS may be considered also from the perspective of an IAH condition [13,14]. The classic triad, including respiratory disorders, decreases in venous return,

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and restriction of internal perfusion is present both in severe OHSS and IAH patients. Several studies related specific indices of the intra-abdominal pressure (IAP) with varying degrees of OHSS [11,15–18].

According to these data, the condition of IAH Grade I in moderate OHSS and IAH Grade II–III in severe OHSS is present [18,19]. Therefore, if we accept the hypothesis that both syndromes are similar, then the principles of OHSS therapy should be consistent with those drawn on the treatment of IAH. For the reasons expressed above, we design the present comprehensive review.

Materials and methods

Information sources

In July 2019, we searched Embase, Medline, and the Cochrane library for all dates up to and including June 2019 to identify potentially relevant publications. In order to maximize the number of publications meeting selection criteria, the medical departments of companies marketing fertility drugs were contacted to request publications related to OHSS which were not identified during the electronic search. Reference lists from studies initially selected and from existing reviews were also searched to identify any additional relevant studies not identified by the electronic searches.

Search strategy

To identify all of the articles assessing OHSS management, the following search strategy was designed: '*ovarian hyperstimulation syndrome management*' ([All Fields] and [MeSH Terms]) or '*intra-abdominal pressure management*' ([All Fields] and [MeSH Terms]) or '*intra-abdominal hypertension syndrome management*' ([All Fields] and [MeSH Terms] or '*methods of reducing intra-abdominal pressure*' [All Fields] and [MeSH Terms]) or '*negative extra-abdominal pressure*' [All Fields] and [MeSH Terms]) and ('humans' [MeSH Terms] and ('women' [MeSH Terms] or 'female' [MeSH Terms]) and 'adult' [MeSH Terms]). This strategy was adapted and applied to different Internet search engines to the MEDLINE database (1966–June 2019). There was no language, type of article or date restriction. This search was further supplemented by a hand-search of reference lists of selected review papers.

Study selection

Titles and abstracts of all the studies retrieved were reviewed by three reviewers (DVM, IAS, EMS) who independently evaluated the eligibility of each manuscripts to initially exclude clearly irrelevant publications. Five per cent of the articles excluded at this point were reviewed by another two reviewer (APP, CCB) to confirm irrelevance. The abstracts of the remaining articles were reevaluated and any designated for exclusion were reviewed and confirmed by a second reviewer. Four reviewers (APP, DVM, IAS, and EMS) extracted the data from the initially selected articles using a prefixed protocol (information was gathered on the characteristics of the participants in the trial, the intervention and how the results were measured). The full text of these articles was obtained and reviewed by all reviewers to ensure they met inclusion criteria. Discrepancies were resolved by consensus or consultation with a third party (CCB) if no agreement could be reached. Finally, CCB checked any possible mistake occurred during the first extraction of data.

Eligibility criteria

Publications were included if the full text of the article was available and data were reported on OHSS with IAH. All types of clinical studies were included. Of the articles reviewed, those that were not related to this specific syndrome, literature reviews not focused on the specific topic or those whose purpose was not to demonstrate a therapeutic impact or management of IAH in OHSS in adult life were not considered. In the final selection of articles only those using diagnostic techniques, treatments or medical procedures that are currently recognized were taken into account.

Results

Study selection

The literature search identified 1362 publications of which 906 citations were initially excluded after a comprehensive evaluation of the abstracts since they were repeated manuscripts, congress abstracts or simply did not accomplish inclusion criteria. Of the 456 articles selected for a full text review, 399 were excluded for the reasons indicated in Figure 1. In total, 51 studies were included in qualitative synthesis.

Study findings

Pathophysiologic treatment for IAP in OHSS

The World Society of Abdominal Compartment Syndrome (WSACS) has published definitions and guidelines for the diagnosis and treatment of patients with IAH and ACS [20]. The WSACS medical management algorithm is based on five treatment options: (1) improvement of abdominal wall compliance;

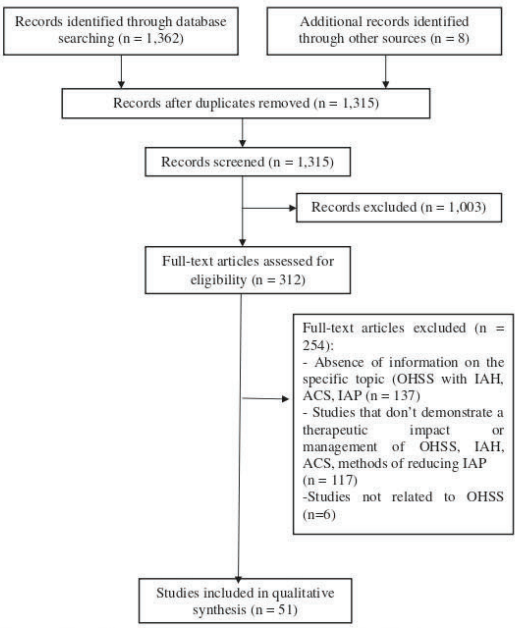

Figure 1. Flow diagram of study selection. *n*: number of publications.

(2) evacuation of intra-luminal contents; (3) evacuation of intra-abdominal space occupying lesions; (4) optimization of fluid management; and (5) optimization of systemic and regional perfusion.

By extrapolating these principles to patients with OHSS, we can understand which methods of reducing IAP are applicable to the treatment of patients with this pathology (Table 1).

Evacuation of intra-luminal contents

Insertion of nasogastric and/or rectal tubes. Using nasogastric and/or rectal tubes, enemas reduce intragastric and, therefore, intra-abdominal volume (IAV), which theoretically should lead to a decrease in IAP. Mahajna et al. described that insertion of a naso-gastric tube immediately resolved the ACS by reducing the IAP from 31 mmHg to normal values [21]. Despite the widespread use of these decompression methods in surgery, no study has yet reported improved outcomes for treating patients with OHSS.

Prokinetics. WSACS recommends the use of prokinetics in patients with elevated IAP. Shaikh et al. [22] described a 36-year-old male with pseudomembranous colitis due to *Clostridium difficile* infection causing ACS with acute kidney injury. After excluding obstruction via computed tomography of the abdomen, neostigmine was given which reduced the IAP from 30 mmHg to 14 mmHg when the patient started to pass stools again. Other prokinetics such as metoclopramide and erythromycin are widely used to treat abdominal distension and ileus. The use of metoclopramide for nausea and vomiting in patients with OHSS is likely to be justified because in the literature there is evidence of the absence of adverse effects of metoclopramide during pregnancy [23].

Evacuation of intra-abdominal space occupying lesions

Surgical decompression is presently an alternative used in the treatment of severe OHSS. Some authors describe a significant improvement of the renal blood flow and an increase of the diuresis after paracentesis or culdocentesis [24–26]. This positive trend can be explained by the effect of a decrease in IAP secondary to fluid removal. However, in most cases, a significant decrease in IAP is only recorded after 2000 or more milliliters of ascites removal. Controversially, an improvement in renal blood flow and urinary function occurred with the removal of much lesser volumes of fluid [27]. These data suggest that the effect of paracentesis depend not on the volume of fluid removed, but rather on the effect of decompression itself.

There are more robust data supporting surgical intervention, such as paracentesis or culdocentesis, than fluid management. According to the authors, after performing cultured enthesis under ultrasound control, the time spent in the hospital is reduced and reproductive results are improved with a significant reduction in the abortion rate [2,28]. Practice Committee of the American Society for Reproductive Medicine recommends paracenteses or culdocenteses for the management of OHSS in an outpatient setting (grade B) [2].

Nevertheless, currently criteria for performing paracentesis are complaints of shortness of breath, abdominal distension, abdominal pain, oliguria, and treatment failure, i.e. already developed multiple organ dysfunction. If OHSS is considered from the perspective of IAH syndrome, then early decompression, even in patients with a moderate form of OHSS, when ascites is not expressed, may be probably justified.

Improvement of abdominal wall compliance

Sedation and analgesia. Only a few studies have investigated the effects of sedation and analgesia on IAP [29,30]. Pain or inflammation can stimulate the tension of the muscles of the anterior abdominal wall, thereby reducing the volume of the chest, pushing the contents of the abdominal cavity, reducing the anterior abdominal wall compliance (C_{ab}) and instantly increasing the IAP. Therefore, sedation and/or analgesia have the potential to reduce IAP. The authors note that the use of epidural anesthesia (EA) has a beneficial effect on the Cab [30–32]. Hakobyan and Mkhoyan [30] compared the effects of EA versus an opioid infusion. In the epidural group, the IAP decreased from 16.8 ± 4.7 mmHg to 6.3 ± 3.1 mmHg, whereas no decrease in IAP was seen in the intravenous opioid group. Some have suggested that opioids could stimulate active phasic expiratory activity, subsequently increasing IAP [33]. However, a recent study in animals did not find such a correlation [34]. We have not found research papers on the use of prolonged EA in patients with OHSS.

Optimization of systemic and regional perfusion

Preventing positive fluid balance also ultimately leads to a decrease in IAV and IAP by reducing the volume of the organ and intestinal edema [31]. This can be achieved using hypertonic albumin, the use of colloids instead of crystalloids, correction of capillary leakage [35]. The authors recognize that excess crystalloid fluids are likely to be central in many cases of IAH/ACS in surgery, and this view coincides with the general trend in resuscitation and intensive care in reducing the infusion of crystalloids and the strategy of applying hemostatic or balanced blood components [36].

In the treatment of OHSS, large volumes of fluid injected and aggressive infusion therapy can provoke an increase in fluid leakage into the abdominal and pleural cavities and contribute to the development and progression of IAH/ACS. After hemodynamic stabilization, normalization of colloid-oncotic plasma pressure and electrolyte disorders, diuresis recovery already in the first hours (days) after hospitalization, it is necessary to drastically reduce the volume of intravenous fluids and begin enteral fluid intake and nutrition [37].

The RCOG (The Management of Ovarian Hyperstimulation Syndrome) states the absence of any studies on the optimal regimen for controlling fluid balance in women with OHSS and recommends using the oral route for hydration whenever possible [7].

Evaluating and maintaining organ function is critical during ongoing medical treatment. Attempts should be made to maintain an abdominal perfusion pressure >60 mmHg with optimal fluid administration [38]. Goal-directed therapy using hemodynamic monitoring is important in this setting.

In general, the topic of optimization of fluid management and systemic and regional perfusion for OHSS is very extensive and, due to space limitations in this article, will be discussed elsewhere.

Table 1. Summary of main studies assessing methods for intra-abdominal pressure reduction.

Author and year of publication	Methods to reduce IAP	Study design	Outcomes	Conclusion
Mahajna et al., 2008 [21]	Insertion of nasogastric tube	Case report. One patient with ACS due to gastric dilatation	IAP decreased from 31 mmHg to normal values	Re-positioning of the nasogastric tube, allowed the decompression of the stomach and the patient's condition immediately improved
Shaikh et al., 2008 [22]	Use of neostigmine as a prokinetic agent	Case report. One patient with ACS due to infection with *Clostridium difficile*	Reduced the IAP from 30 mmHg to 14 mmHg	*Clostridium difficile* colitis can cause IAH and ACS. Rapid diagnosis, early aggressive supportive care, metronidazole and prokinetics are necessary to lower the morbidity and mortality of *Clostridium difficile* colitis associated with IAH and ACS
Maslovitz et al., 2004 [27]	Paracentesis	Clinical trial involving 19 women with severe OHSS, manifested by free peritoneal fluid	An average of 3340 mL of ascitic fluid was drained. IAP decreased from 17.5 ± 1.24 cmH_2O to 10 ± 1.22 cmH_2O. Urine output was increased (by 65%, from 925 ± 248 mL/d before paracentesis to 1523 ± 526 mL/d on the day after paracentesis, $p < .001$)	Paracentesis lowered IAP and decreased renal arterial resistance, ultimately resulting in increased urine production. It is plausible that the beneficial effects of paracentesis on urine output in OHSS are due to improved renal blood flow from a direct decompression effect
Tasdogan et al., 2009 [29]	Sedation and analgesia	Prospective, single-center study involving 40patients with severe sepsis after abdominal surgery. Comparison of the effects of an intravenous infusion of propofol and the dexmedetomidine	IAP was significantly lower at the 24th hour (12.35 ± 5.84 mmHg vs. 18.1 ± 2.84 mmHg, respectively) and the 48th hour (13.9 ± 6.15 mmHg vs. 18.7 ± 3.46 mmHg, respectively) in dexmedetomidine group	Dexmedetomidine infusion decreases TNF-a, IL-1, and IL-6 levels and IAP more than a propofol infusion
Hakobyan and Mkhoyan, 2008 [30]	Analgesia	Blinded prospective study involving critically-ill surgical patients with primary IAH received postoperative thoracic epidural analgesia ($n = 58$) or intravenous opioid analgesia ($n = 130$)	IAP decreased from 16.82 ± 4.56 to 6.30 ± 3.11 mmHg in theepidural group There were no significant differences of IAP and APP in the opioid group	Continuous thoracic epidural analgesia decreases IAP and improves APP without hemodynamic compromise in postoperative critically-ill patients with primary IAH
Cordemans et al., 2012 [35]	Aiming for a negative fluid balance	Retrospective matched case-control study involving 114 mechanically ventilated patients with ALI receiving PAL-treatment	After 1 week, PAL-treated patients had a greater reduction of EVLWI, IAP, and cumulative fluid balance (-4.2 ± 5.6 vs. -1.1 ± 3.7 mL/kg, $p = .006$; -0.4 ± 3.6 vs. 1.8 ± 3.8 mmHg, $p = .007$; -1451 ± 7761 vs. 8027 ± 5254 mL, $p < .001$)	PAL-treatment in patients with ALI is associated with a negative fluid balance, a reduction of EVLWI and IAP, and improved clinical outcomes without compromising organ function
Sugerman et al., 2001 [42]	CNAP	Short-term clinical intervention trial involving 7 centrally obese women with PTC	IAP decreased from 19.1 ± 3 to 12.5 ± 2.8 cmH_2O ($p < .001$).There was a decrease in both headache (6.8 ± 0.8 to 4.2 ± 0.8, $p < .05$) and pulsatile tinnitus (4.2 ± 0.5 to 1.8 ± 0.5, $p < .02$) within 5 min, and in headache (to 2.2 ± 0.8, $p < .01$) and tinnitus (to 1.7 ± 0.5, $p < .01$) within 1 h of device activation	Decreasing IAP relieved headaches and pulsatile tinnitus in PTC
Valenza et al., 2003 [43]	CNAP	Clinical trial involving 30 critically-ill patients	Basal IAP ranged from 4 to 22 mmHg. NEXAP decreased IAP from 8.7 ± 4.3 mmHg to 6 ± 4.2 (basal vs. NEXAP0 $p < .001$). There was a further decrease of IAP when more negative pressure was applied: 4.3 ± 3.2 mmHg, 3.8 ± 3.7 mmHg (NEXAP-5 and NEXAP-10 vs. NEXAP0, respectively, $p < .001$). Cardiac output did not significantly change with NEXAP	NEXAP may be applied in critically ill patients to decrease IAP noninvasively
Pracca et al., 2011 [45]	CNAP	Clinical trial involving 4 critically-ill patients	IAP decreasedfrom 12.7 to 9.3 mmHg	ABDOPRE may be useful in clinical practice for the reduction of intra-abdominal pressure

IAP: intra-abdominal pressure; ACS: abdominal compartment syndrome; IAH: intra-abdominal hypertension; OHSS: ovarian hyperstimulation syndrome; TNF-a: tumor necrosis factor alpha; IL: interleukin; APP: abdominal perfusion pressure; ALI: acute lung injury; EVLWI: extravascular lung water index; PAL-treatment: combines high levels of positive end-expiratory pressure, small volume resuscitation with hyperoncotic albumin, and fluid removal with furosemide or ultrafiltration; PTC: *Pseudotumor cerebri*; CNAP: continuous negative extra-abdominal pressure; NEXAP: negative extra-abdominal pressure; ABDOPRE: short for ABDOminal PREssure.

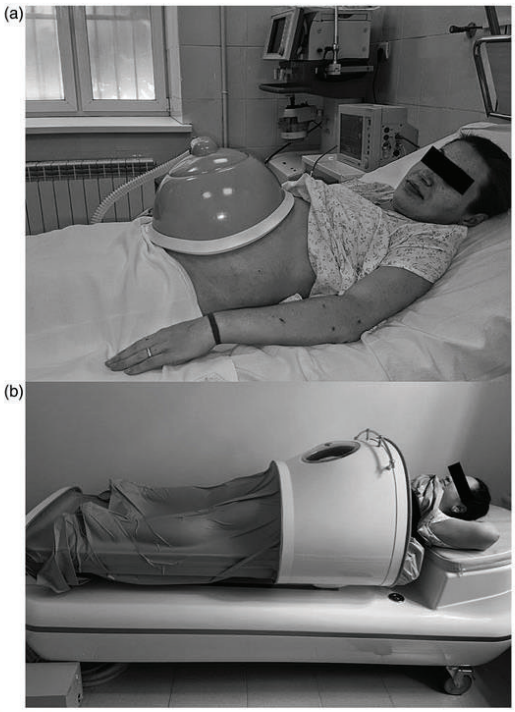

Figure 2. Continuous negative extra-abdominal pressure methods for reducing intra-abdominal hypertension. (a) Abdominal decompressor LOCAD (short for LOCal Abdominal Decompressor); (b) KAD-01-ACS "The hope".

New medical treatment options

Continuous negative extra-abdominal pressure. The procedure of continuous negative extra-abdominal pressure (CNAP) is one of the future promising options for noninvasive treatment of IAH/ACS [39]. Scientific studies on the physiological effects of localized decompression began in 1959 with a method for abdominal decompression anticipated by Heyns [40]. The device was a sealed chamber superimposed on the patient's abdomen and a vacuum pump for the local depositing. Noteworthily, the history of abdominal decompression is a typical example in the history of medical innovations: the description of the phenomena, its silencing, the rediscovery of the previously described phenomena, skepticism in relation to already known facts and its subsequent acceptance. The initial studies were carried out decades ago before the standard use of Doppler ultrasound as a diagnostic tool; consequently, the practical implementation of such method was ahead of the development of its theoretical justification.

Later, many modifications of abdominal decompression apparatus were created, representing a sealed chamber superimposed on the patient's abdomen and a vacuum pump. Bloomfield et al. [41] in animal experiments showed a significant decrease in IAP when applying continuous negative pressure through a large poncho connected to a vacuum. The mean IAP decreased from 30.7 ± 1.3 to 18.2 ± 1.3 mmHg. They also found reduced central venous, inferior vena cava, and intracranial pressures when CNAP was applied. Sugerman et al. [42] showed a decrease in IAP from 19.1 ± 3 to 12.5 ± 2.8 cm H_2O and the disappearance of headaches and pulsating tinnitus in seven patients with *Pseudotumor cerebri* using CNAP. Valenza et al. [43] performed the CNAP procedure in 30 patients, and showed that, when creating a negative pressure of 5 cm H_2O, IAP decreased from 8.7 ± 4.3 to 4.3 ± 3.2 mmHg, with a negative pressure of 10 cm H_2O – up to 3.8 ± 3.7 mmHg. Hence, the more negative pressure was applied, the more IAP was reduced. The authors found the effectiveness of CNAP in reducing not only IAP, but also intracranial and pleural pressure with subsequent improvement of lung volumes and chest elasticity [44], but the common drawback for the CNAP devices is the occasional incompatibility between the dimensions of the chamber and patient's anatomy. For example, a study using the device for reducing abdominal pressure in four critically ill patients was published in 2011 [45], as a result of which in three patients the average percentage reduction in IAP was 25.3%, and in a patient with obesity increased by 38%.

This was explained by the 'ventilation system effect', which developed due to an insufficient proportion between the glass chamber and the abdominal wall, as a result of which the IAV was reduced due to the intromission of a part of the abdominal wall into the chamber as represented in Figure 2(a).

A modern equipment for abdominal decompression (KAD-01-ACS known as 'The hope', Figure 2(b)) has been developed in St. Petersburg (Russia) to avoid these drawbacks. The experience using this equipment showed the high efficiency of NEXAP in the treatment of different women's reproductive health conditions [46–49].

Only two studies on abdominal decompression are recorded in the Cochrane Database. One of them states that there is no benefit from the prophylactic use of abdominal decompression in healthy pregnancies [50]. On the contrary, in the second one including pregnant women having preeclampsia a positive therapeutic effect was demonstrated [51].

All these studies have shown that CNAP applied to the abdomen, reduces IAP with minimal effects from mean arterial pressure and cardiac output and is simple and easy to apply with minimal discomfort to the patient. Considering OHSS as a polycompartmental syndrome, CNAP may be used in its treatment as early as possible to prevent further organ dysfunction and to avoid the transition to a severe stage of IAH and ACS.

Conclusions

This systematic review and analysis of the literature supports the hypothesis of the potential role of IAH in the development of medium and severe forms of OHSS and considers the prospects for using methods to reduce IAP in its management. Well-known therapeutic measures, such as: sedation and analgesia, prescription of prokinetics, nasogastric tube, rectal tube, enema, reduction of aggressive infusion therapy, paracentesis, or culdocentesis might be used in the treatment of OHSS according to the general principles of intensive therapy and, for ascertaining increased abdominal pressure should be started early to prevent further organ dysfunction and to avoid the transition to a more severe stage of IAH and ACS.

The procedure of CNAP could be a promising option in the pathogenetic treatment of IAH, but so far it has not been used in the treatment of OHSS. In spite of the benefits showed in the initial studies, there are a large number of emerging questions that embrace the safety of continuous negative extra-abdominal pressure methods, the need to implement continuous monitoring of IAP; the severity of OHSS at which continuous negative extra-

abdominal pressure should be indicated, the question of the negative pressure and others related to the procedure itself. All these issues are grounds for future research in this area.

Disclosure statement

The authors declare no conflict of interest.

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Working Hypothesis

Intra-abdominal hypertension may play a role in the development of the severe forms of OHSS and in its complications. Moderate and severe OHSS with organ dysfunction would have the same pathophysiology and clinical features as intra-abdominal hypertension syndrome; therefore, the treatment of the moderate and severe forms of OHSS should include the principles of therapy for intra-abdominal hypertension syndrome.

Objectives

- To analyze clinical history records, laboratory and functional risk factors for the development of severe forms of OHSS (Article 3,4).
- To study the indices of intra-abdominal pressure in women with various degrees of OHSS and to determine their clinical value (Article 3).
- To study the dynamics and relationship of indicators of ovarian volume, ascites and intra-abdominal pressure with varying degrees of severity of OHSS (Article 3).
- To assess the usefulness of various anthropometric indicators in determining the severity of OHSS (Article 4).
- To develop indications and additional indicators for paracentesis based on the data from the present studies (Article 3,4).
- To assess the diagnostic value of intra-abdominal hypertension as a criterion for the severity of OHSS (Article 3,4).
- To assess the usefulness of intra-abdominal hypertension to predict the progression and outcomes of OHSS (Article 3,4).
- To demonstrate a plausible relation between changes observed in intra-abdominal hypertension with the effectiveness of treatment (Article 3,4).

Investigations conducted

Material and Methods

Obtained Results

Sample

A total of 76 infertile women who were in an in vitro fertilization program and presented OHSS were included in this study. Sample size was established based on the fact that according to the Ministry of Health of the Saratov Region, during the period from 2015 to 2019, 4800 cycles of ART were performed in all medical institutions of the region. Complications presented by various forms of OHSS requiring outpatient monitoring and hospitalization, were recorded in 95 cases (1.9%). Thus, using the statistical software to calculate the sample size with a 5% maximum acceptable error, 95% confidence level, we obtained a sample size of 76 women with OHSS. All of them were admitted into the gynaecological department of the city clinical hospital No.1 named after Yu.Ya. Gordeev (Saratov, Russian Federation). Data regarding patients' baseline characteristics are summarized in Table S3 (*Supplemental materials*). Anthropometrical, laboratory and clinical data were recorded in all included subjects (Table S4,S5 *Supplemental materials*). The age range of the study participants was from 20 to 40 years old and the body mass index (BMI) was from 16,9 to 24,1 kg/m^2.

OHSS was classified according to the Royal College of Obstetricians & Gynaecologists guidelines [25]. Therefore, patients were allocated into four groups depending on the severity of OHSS: mild OHSS (group I, n = 25), moderate OHSS (group II, n = 25), severe OHSS (group III, n = 21), and critical OHSS (group IV, n = 5). Early-onset OHSS was defined when the syndrome was initiated during the first 9 days after trigger administration of hCG, and late OHSS was defined when the syndrome was initiated from 10 days after. The current study included 19 (25%) women with early OHSS and 57 (75%) women with late OHSS. The IAP was measured 4 [IQR, 3–5] days after hCG administration in case of early OHSS and 17 [IQR, 13–19] days after hCG triggering in case of late OHSS. The average length of stay for subjects with early OHSS was 10 [IQR, 7–12] days; the average length of a hospital stay for women with late OHSS was 9 [IQR, 7–11] days.

All women admitted with the diagnosis of OHSS were considered for inclusion in the study. Those who voluntarily refused to participate were excluded.

Procedures

All the enrolled women underwent clinical examination including height, body weight, abdominal circumference, dehydration assessment, oedema, heart rate, respiratory rate, blood pressure, and diuresis. Body mass index was assessed using the Quetelet's equation, and routine laboratory tests were performed in all cases (Table S1 *Supplemental materials*). Anthropometrical and clinical data were recorded in all included subjects. The anteroposterior diameter of the abdomen (APD) and transverse diameter of the abdomen (TS) were measured with a pelvimeter. The APD was defined as the distance between the spine at the L 3-4 level and the abdomen apex, then the pelvimeter branches were rotated in the same plane, set along the midaxillary lines, and after that, TS measurement was made. The APD/TS ratio was calculated.

Ultrasound measurement of the ovarian size and pelvic and abdominal free fluid was done (Accuvix XG [Samsung MEDISON Co. Ltd. Korea]) using 3.5 MHz sectoral sensors. Ovarian volume was set using the prolate ellipsoid formula (height × width × depth × 0.523).

Ascites index (AsI) was used to determine the quantitative assessment of ascites using a convex probe in the supine position on the external abdominal quadrants including inguinal regions and the liver and spleen areas. The depth of the largest free fluid pocket in the horizontal plane, perpendicularly to the abdominal circumference tangent line in each quadrant (in mm), is added in an analogous manner to the amniotic fluid index determined in pregnant women.

Method for Measuring Intra-abdominal Pressure

IAP was measured through a Foley catheter using a pressure transducer [42]. To minimize discomfort during the procedure, before the introduction of the catheter, a sterile gel of Cathejell lidocaine® (Pharmazeutische Fabrik Montavit Ges.m.b.H. Salzbergstrasse 966060 Absam/Tirol Austria) was applied to the urethra and the

end of the catheter, which has an antimicrobial and local anaesthetic effect. Transducer was zeroed at the level ofmidaxillary line at the iliac crest. The IAP was recorded during end expiration after injecting 25 ml of saline into the bladder with patient in supine position. For checking that the pressure signal was correctly transduced, gentle compressions of the abdomen were seen to cause instant oscillation in the IAP tracing. If the signal appeared damped, the Foley catheter was opened to flush out airway bubbles and the procedure repeated.

The severity of IAH was quantified as grade I (12–15 mmHg), grade II (16–20 mmHg), grade III (21–25 mmHg), or grade IV (> 25 mmHg) [42].

Statistical Analysis

The data were analysed using a personal computer-based software package (SPSS 26.0, SPSS Inc. Headquarters, 233 South Wacker Drive, 11th Floor, Chicago, IL 60606, USA). The Shapiro-Wilk test was used to determine the normal distribution of the sample. Data for non-normally distributed variables are given as the median [interquartile range]. Homogeneity of within-group variances was evaluated by Levene's test. The Kruskal-Wallis test was used to analyse differences between groups. Statistically significant results were followed by Mann-Whitney U-tests with Bonferroni adjustment to detect subgroup differences. Spearman’s correlation coefficients were used to check the association between continuous variables. All probability tests were two-sided and a p-value of <0.05 was considered significant.

Article 4

Assessing the Usefulness of Severity Markers in Women with Ovarian Hyperstimulation Syndrome.

Petrenko AP, Castelo-Branco C, Marshalov DV, Kuligin AV, Shifman EM, Nesnova ES. has been published in **Reproductive sciences**

The development of moderate, severe, and critical ovarian hyperstimulation syndrome is accompanied by an increase in intra-abdominal volume and intra-abdominal hypertension. Assessing the dynamics of ovarian volume, ascites index and intra-abdominal pressure could be a useful tool in defining the severity of ovarian hyperstimulation syndrome.

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REPRODUCTIVE ENDOCRINOLOGY: ORIGINAL ARTICLE

Assessing the Usefulness of Severity Markers in Women with Ovarian Hyperstimulation Syndrome

Aleksei Petrovich Petrenko[1,2,3] · Camil Castelo-Branco[1] · Dimitry Vasilevich Marshalov[2,3] · Alexander Valerievich Kuligin[2] · Efim Munevich Shifman[4] · Elena Sergeevna Nesnova[3,5]

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Abstract

The present study aims to assess the usefulness of severity markers in women with ovarian hyperstimulation syndrome (OHSS). An observational study was designed including 76 women with varying degrees of severity of OHSS. Clinical history, physical examination, laboratory tests, and ultrasound measurement of the ovarian size and ascites index were carried out in all patients. Intra-abdominal pressure (IAP) was measured using an intravesical Foley Manometer catheter. Ascites index and ovarian volume increased progressively being highest in the most severe stage of OHSS. The median IAP in mild OHSS was found to be lower than that in the moderate and severe OHSS (4.0 mm, 12 mm, and 16.0 mm, respectively). Critical cases of OHSS presented the highest IAP (25.0 mm). IAP did not reach the level of intra-abdominal hypertension in mild OHSS, whereas moderate and severe OHSS was associated with intra-abdominal hypertension grade I and grade II–III, respectively. Values of IAP in critical OHSS were found similar to those observed in abdominal compartment syndrome patients. The IAP showed a strong positive correlation with ovarian volume and ascites index. The reduction of IAP after paracentesis was greater among critical OHSS patients. The ovarian volume and the level of intra-abdominal hypertension are related to the severity of OHSS and are of particular importance in the initialization of the syndrome. Ascites index is simple and convenient and can serve as an indirect marker of the abdominal reserve volume. In conjunction with clinical and laboratory data, ascites index and IAP values might be indicators for paracentesis.

Keywords Ovarian hyperstimulation syndrome · Intra-abdominal pressure · Intra-abdominal hypertension · Ovarian volume · Ascites index

The study was registered at the ISRCTN registry; identifier: ISRCTN66235250, http://www.isrctn.com/ISRCTN66235250 and https://doi.org/10.1186/ISRCTN66235250

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most severe and potentially life-threatening iatrogenic complication associated with assisted reproduction techniques [1, 2]. The OHSS clinic is characterized by ovarian enlargement, fluid shifts into the third space, hypovolemia, haemoconcentration, serosae effusions, ascites, hypercoagulation, renal failure, and multiple organ failure in severe cases [3, 4]. There is no specific treatment for OHSS, and management is based on the control of fluid balance, thromboembolic prophylaxis, and paracentesis or thoracentesis when needed [5, 6].

It is a well-known fact that pathophysiology and clinic of moderate and severe forms of OHSS are almost identical to those of intra-abdominal hypertension syndrome (IAH) [7–9]. Data suggest that intense ascites with IAH can lead to abdominal compartment syndrome (ACS) and associated severe organ dysfunction, which is a main factor for unfavourable outcome in women with OHSS [10, 11]. According to the World Society of Abdominal Compartment Syndrome (WSACS), intra-abdominal pressure (IAP) is determined by two elements—the intra-abdominal volume (IAV) and compliance of the abdominal wall [12]. In OHSS, the main factors related to the increase of the non-compressible IAV and, consequently, IAP are ovarian enlargement and ascites progression [13, 14]. Currently, only few reports have been published measuring the level of IAP in OHSS. [10, 15–17]. The aim of the present study is the assessment of the usefulness of different markers of severity such as IAP, ovarian volume (OV), and ascites in women with OHSS.

Methods

Sample

The sample comprised a total of 76 women who were admitted into the Gynaecological Department of the City Clinical Hospital No.1 named after Yu.Ya. Gordeev (Saratov, Russian Federation) with the diagnosis of OHSS during the period from 2015 to 2019. All women complaining with infertility were in an in vitro fertilization program (IVF). The severity of OHSS was classified into mild, moderate, severe, and critical, based on guidelines of Royal College of Obstetricians & Gynaecologists [14]. According to the described criteria, all women were divided into four groups depending on the severity of OHSS. Group I included women with mild OHSS ($n = 25$), group II—moderate OHSS ($n = 25$), group III—severe OHSS ($n = 21$), and group IV—critical OHSS ($n = 5$).

Early-onset OHSS was defined when the syndrome was initiated during the first 9 days after trigger administration of hCG, and late OHSS was defined when the syndrome was initiated from 10 days after. All women admitted to the hospital with clinical evidence of OHSS were asked to take part in the study. Exclusion criteria comprised women who voluntarily refused to participate in the study.

Procedures

All the enrolled women underwent clinical examination including height, body weight, abdominal circumference, dehydration assessment, oedema, heart rate, respiratory rate, blood pressure, and diuresis. Body mass index was assessed using the Quetelet's equation, and routine laboratory tests were performed in all cases (Table S1). Ultrasound measurement of the ovarian size and pelvic and abdominal free fluid was done (Accuvix XG [Samsung MEDISON Co. Ltd. Korea]) using 3.5 MHz sectoral sensors. Ovarian volume was set using the prolate ellipsoid formula (height × width × depth × 0.523) [18].

Ascites index (AsI) was used to determine the quantitative assessment of ascites [19] using a convex probe in the supine position on the external abdominal quadrants including inguinal regions and the liver and spleen areas. The depth of the largest free fluid pocket in the horizontal plane, perpendicularly to the abdominal circumference tangent line in each quadrant (in mm), is added in an analogous manner to the amniotic fluid index determined in pregnant women.

Method for Measuring Intra-abdominal Pressure

IAP was measured through a Foley catheter using a pressure transducer [20]. To minimize discomfort during the procedure, before the introduction of the catheter, a sterile gel of Cathejell lidocaine® (Pharmazeutische Fabrik Montavit Ges.m.b.H. Salzbergstrasse 966060 Absam/Tirol Austria) was applied to the urethra and the end of the catheter, which has an antimicrobial and local anaesthetic effect. Transducer was zeroed at the level of midaxillary line at the iliac crest. The IAP was recorded during end expiration after injecting 25 ml of saline into the bladder with patient in supine position. For checking that the pressure signal was correctly transduced, gentle compressions of the abdomen were seen to cause instant oscillation in the IAP tracing. If the signal appeared damped, the Foley catheter was opened to flush out airway bubbles and the procedure repeated.

The severity of IAH was quantified as grade I (12–15 mmHg), grade II (16–20 mmHg), grade III (21–25 mmHg), or grade IV (> 25 mmHg) [20].

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics Version 26 (SPSS Inc., USA). Results of measurement were initially analysed using Shapiro-Wilk test for normal distribution. The data were expressed as the median [interquartile

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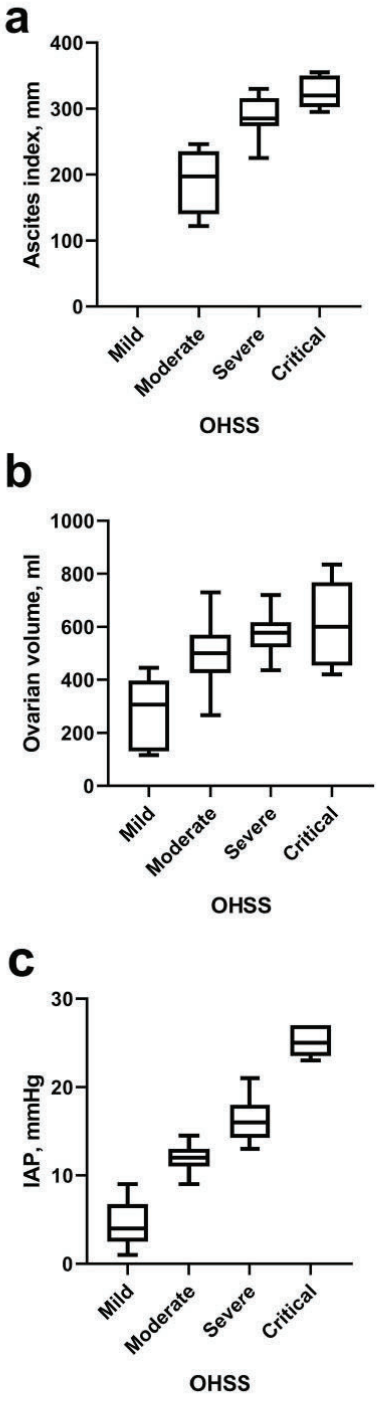

Fig. 1 Box plots of ascites index (**a**), ovarian volumes (**b**), and intra-abdominal pressure (**c**) according to severity of ovarian hyperstimulation syndrome. The horizontal line within the box indicates the median, the box represents the interquartile range, and the whiskers above and below the box extend to the highest and lowest values, respectively

range] in the non-normally distributed variables. Homogeneity of within-group variances was evaluated by Levene's test. Differences between more than two groups were assessed with Kruskal-Wallis test. Statistically significant results were followed by Mann-Whitney *U* tests with Bonferroni adjustment to detect subgroup differences. The association between continuous variables were assessed through the use of Spearman's correlation coefficients. The categorical variables were compared with Pearson's Chi-square test. All probability tests were two-sided, and a p value of < 0.05 was considered significant.

Results

The median [interquartile range (IQR)] age of study participants was 30 [IQR, 27–34] years. The average body mass index (BMI) for the whole cohort was 20.6 [IQR, 19.7–21.1] kg/m^2.

The current study included 19 (25%) women with early OHSS and 57 (75%) women with late OHSS. In participants with early-onset OHSS, the severity of the disease was classified as mild in 7 (37%) cases, moderate in 4 (21%) cases, severe in 6 (32%) cases, and critical in 2 (10%) cases. Of those women who were admitted with late OHSS, 18 (32%) had mild OHSS, 21 (37%) had moderate OHSS, 15 (26%) had severe OHSS, and 3 (5%) had critical OHSS. Comparison of rates was performed by Pearson's Chi-square test. In the present study, the OHSS severity was not significantly different between the early and late OHSS groups ($p > 0.05$).

The IAP was measured 4 [IQR, 3–5] days after hCG administration in case of early OHSS and 17 [IQR, 13–19] days after hCG triggering in case of late OHSS.

The average length of stay for subjects with early OHSS was 10 [IQR, 7–12] days; the average length of a hospital stay for women with late OHSS was 9 [IQR, 7–11] days.

As expected, the ascites index increased progressively and tended to be the highest in the most symptomatic stage of OHSS (Kruskal-Wallis test, $p < 0.001$). Figure 1a represents the intergroup comparison of AsI. The median AsI was significantly lower in patients with moderate OHSS (197 mm [IQR, 140–235]) compared with severe OHSS (285 mm [IQR, 276–321]; $p < 0.001$) or critical OHSS (320 mm [IQR, 310–346]; $p < 0.001$). However, there was no significant difference in AsI between severe and critical OHSS groups (Table S2).

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Similarly, the ovarian volume showed a significant increase (Kruskal-Wallis test, $p < 0.001$, Fig. 1b). The median OV in mild OHSS cases (307 ml [IQR, 132–392]) was significantly different from that of moderate (500 ml [IQR, 441–561]; $p < 0.001$), severe (578 ml [IQR, 533–611]; $p < 0.001$), and critical OHSS (600 ml [IQR, 487–704]; $p < 0.001$). No significant differences were found in OV between moderate, severe, and critical OHSS groups.

IAP studies demonstrated significant differences between groups, as analysed using Kruskal-Wallis test ($p < 0.001$). In comparing each two groups, the median IAP of the mild OHSS group (4.0 mmHg [IQR, 3.0–6.5]) was found to be significantly lower than that of the moderate (12.0 mmHg [IQR, 11.0–13.0], $p < 0.001$), severe (16.0 mmHg [IQR, 14.5–18.0], $p < 0.001$), and critical OHSS groups (25.0 mmHg [IQR, 24.0–27.0], $p < 0.001$). Moreover, there was a significant difference between the moderate and the severe ($p < 0.01$) and critical OHSS groups ($p < 0.01$). Although there was a considerable increase of IAP in the critical OHSS, this group was not statistically different from the severe OHSS group (Fig. 1c). As evidenced above, deteriorating clinical status is associated with a significant increase of OV, AsI, and IAP.

The median AsI was significantly higher in patients with respiratory insufficiency (298 mm [IQR, 278–316]) compared with subjects without dyspnoea (239 mm [IQR, 192–280]; $p < 0.01$). Similarly, the IAP in women with respiratory failure (17.75 mmHg [IQR, 16.50–24.50]) was significantly different from that in patients without breathlessness (11.0 mmHg [IQR, 5.25–13.75], $p < 0.001$).

The median IAP in women with abdominal bloating, nausea, or vomiting (13.5 mmHg [IQR, 12.0–17.0]) was found to be significantly higher than that in persons without abdominal discomfort (3.5 mmHg [IQR, 2.0–5.0], $p < 0.001$). As expected, all patients with ascites reported gastrointestinal symptoms.

Oliguria was associated with considerable increase in AsI (289 mm [IQR, 271–316]) and IAP (17.0 mmHg [IQR, 14.50–19.25]) compared with normal renal function (median AsI—196 mm [IQR, 140–235]), median IAP—8.5 mmHg [IQR, 4.0–12.0] $p < 0.001$).

Correlation analysis was used to identify whether the level of IAP was independently associated with AsI and OV. As we anticipated, there was a strong positive correlation between the OV and IAP (Spearman's $r = 0.699$, $p < 0.001$; Fig. 2a). Besides that, the IAP showed a significant positive correlation with the AsI (Spearman's $r = 0.695$, $p < 0.001$; Fig. 2b).

The management of severe and critical OHSS includes reduction of IAP by paracentesis. The above-mentioned measurement methods were used in seven women with the indications for paracentesis before and 30 min after procedure. An average of 2 l of ascitic fluid was removed from each patient in one sitting. The reduction of IAP after this procedure was greater among critical OHSS patients (Fig. 3a). These results are in line with the changes observed in the AsI after paracentesis (Fig. 3b).

Discussion

Based on the time of onset of symptoms after trigger administration, we divided women into two groups: with early and late development of OHSS. "Early" OHSS usually develops within 9 days after the hCG injection and is mainly associated with ovarian overreaction. "Late" OHSS commonly appears 10 days or more after the injection of hCG and is usually the result of endogenous hCG from early pregnancy [14]. According to the literature, there is contradictory information about the relationship between the time of onset and the severity of OHSS. Some sources claim that late OHSS, as a rule, is longer and more severe than its early form [21]; others argue that there is no difference [22]. In the present study, we did not find a statistically significant association between the type of OHSS and its severity.

There are scant data on IAP levels in women with OHSS and most with small sample size [10, 13, 15–17, 23]. Just in three case reports of severe OHSS, the authors recorded IAP numbers meeting ACS criteria [10, 17, 23]. It is to note the study by Maslovitz S. et al. including 19 patients, which shown that an average IAP of 17.5 ± 1.24 cm H2O is related to various symptoms, including decreased respiratory function, intense ascites, and oliguria [15].

In the present study assessing the level of IAP in 76 women with different degrees of OHSS, the median value of IAP did not reach levels of IAH in cases of mild OHSS, while moderate OHSS was associated with IAH grade I, and severe OHSS was related to II–III IAH grade according to WSACS classification. The relationship between IAP and OHSS severity is highly significant. The higher the IAP, the greater the severity. Mild OHSS is related to a slight increase in IAP. In moderate OHSS, ascitic fluid accumulates and the ovaries continue to grow, but the abdominal cavity still adapts and IAP grows moderately. When transition to severe OHSS occurs, the reserve volume of the abdominal cavity is close to minimum values and the extensibility of the anterior abdominal wall is depleted, which results in a linear rapid increase in IAP. Lastly, in critical OHSS, with the addition of a minimum amount of liquid, an explosive increase in IAP is observed. In critical OHSS, IAP values exceed 25 mmHg, and an explicit ACS develops with rapid progression to multiple organ failure. Our data are consistent with those by Shay S et al., who also noted the nonlinearity of the increase in IAP in patients with chronic dialysis [24].

Indications for paracentesis according to the guidelines of the Royal College of Obstetricians and Gynaecologists [14] include (a) severe abdominal distension and abdominal pain

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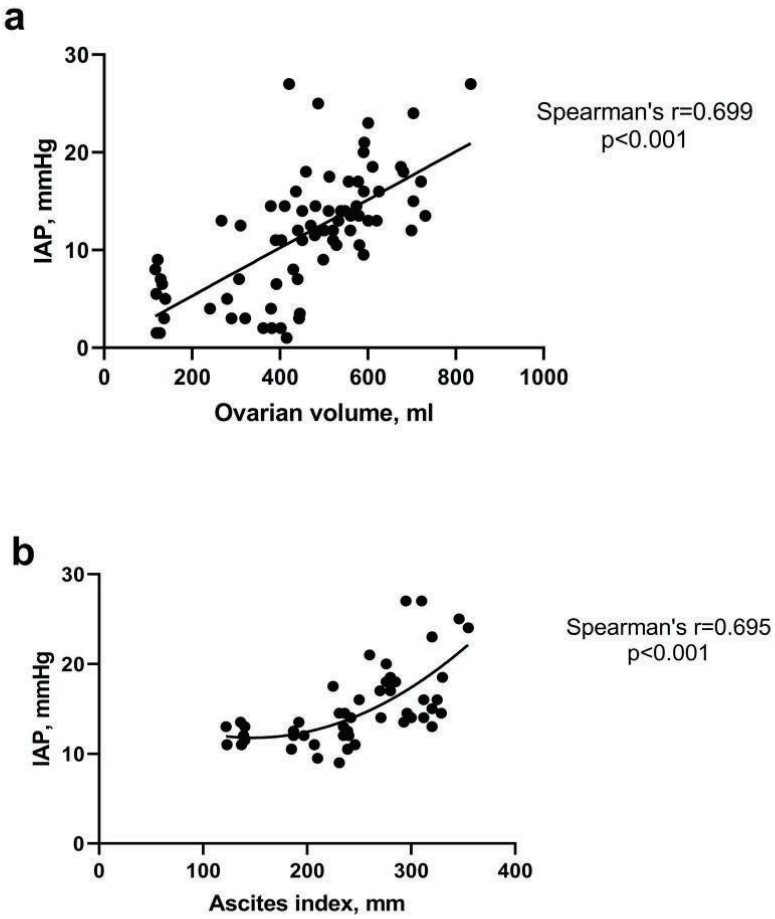

Fig. 2 Scatter plots of intra-abdominal pressure related to ovarian volumes (**a**) and ascites index (**b**)

secondary to ascites, (b) shortness of breath and respiratory compromise secondary to ascites and increased intra-abdominal pressure, and (c) oliguria despite adequate volume replacement, secondary to increased abdominal pressure causing reduced renal perfusion. It is to note that in this guideline, IAP is mentioned in two of the three indications for paracentesis; however, there are no recommendations for monitoring it. Based on this fact, it can be ensured that in many cases of severe and critical OHSS, the ACS was underdiagnosed because routine IAP measurements are usually ruled out by many departments of gynaecology and ICUs and paracentesis is performed in patients with life-threatening conditions, that is, with already developed severe multiple organ dysfunction.

Current evidence directly associates the progressive increase in OV with the severity of OHSS. Abbara and colleagues found that no patient with a mean OV < 100 ml was diagnosed with moderate to severe OHSS, whereas 16% of patients with OV between 101 and 200 ml and 56% of patients with OV > 200 ml were diagnosed with this condition [18]. OV was larger in patients with more symptomatic OHSS and in patients with increased ascitic volume. Our data confirms the relationship between OHSS severity and IAP with OV values: larger OV is associated with more severe OHSS (Fig. 2) and higher IAP. Nevertheless, it should be noted that the maximum increase in OV is observed between groups I and II, and as the OHSS severity increases, OV growth slows down, which indicates the significance of the increase in OV in the initialization of the OHSS. These findings are consistent with published data on the pathogenesis of OHSS as a result from the release of vasoactive substances from the ovary, such as vascular endothelial growth factor (VEGF A) and vascular permeability factor (VPF), due to excessive stimulation ovaries after the start of egg maturation during IVF treatment.

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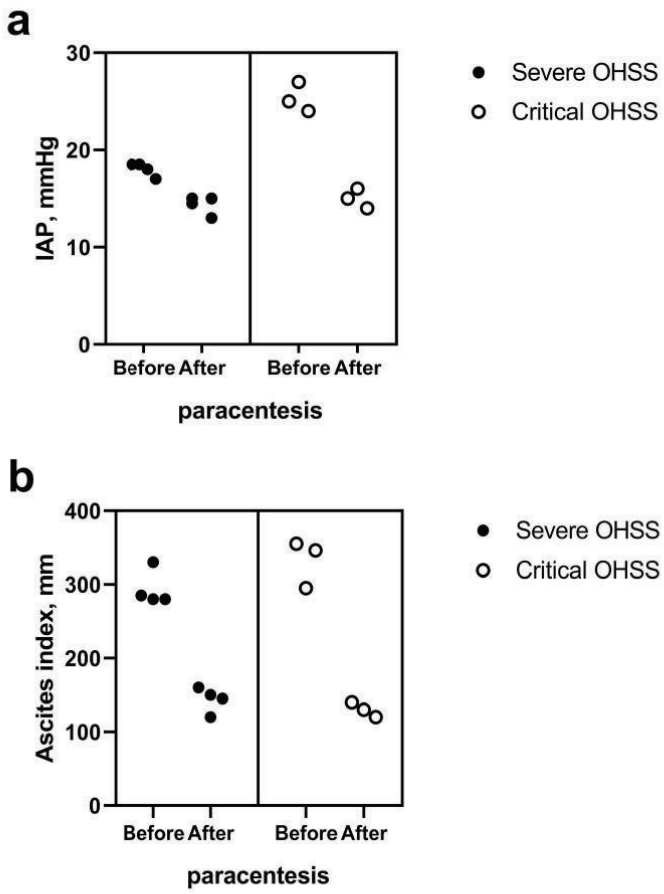

Fig. 3 The intra-abdominal pressure (**a**) and ascites index (**b**) according to severity of ovarian hyperstimulation syndrome before and after paracentesis

This leads to an increase in the permeability of capillaries and the movement of fluid from the intravascular compartment into the third space of the body [25, 26].

Tense ascites and accompanying IAH in OHSS are well-known facts [7, 8, 27]. Diagnosis of ascites based on complaints, physical methods, or ultrasound investigation is not problematic, but quantitative assessment of its amount is a difficult task. Physical methods of ascites monitoring used to date include sequential measurements of body weight, abdominal circumference, and determination of the protrusion index; however, such methods are often inaccurate and based on subjective interpretation. The indicator-dilution technique may be used for calculating the ascites volume, but it carries a risk of infection, bowel perforation, or haemorrhage [28]. Computed tomography enables to use 3D-rendering method for calculating the volume of ascites and allows to get the most reliable data, but this is an expensive method that requires an appropriate equipment [29]. From a clinical point of view, there is no need to know the exact amount of fluid in the abdominal cavity; what is important is to promptly establish indications for paracentesis in order to prevent further organ dysfunction and avoid the transition to a more severe stage of IAH and ACS.

In our study, we determined AsI by ultrasound, which is a simple and quick method to assess the degree of ascites. As Fig. 1 shows, there is a large increase in AsI indices between groups II and III. The abdominal cavity can still adapt to a certain amount of ascitic fluid. Then the reserve volume of the abdominal cavity and the extensibility of the anterior abdominal wall are depleted, and with a slight increase in AsI, a transition to critical OHSS with a progressive increase in IAH is visible. On the other hand, the higher IAP and AsI values before paracentesis, the stronger their decrease after drainage. Thus, the AsI can be considered an indirect indicator of the reserve volume of the abdominal cavity, that is, the volume that can be added to the basic IAV without the

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development of systemic dysfunctions associated with the growth of IAP.

In severe OHSS, when in most cases there are indications for paracentesis, the average AsI was 285 mm (276–312 mm). Our data is consistent with those from the study by Szkodziak P et al., who concluded that women with severe OHSS required decompressive paracentesis when median AsI was above 290 mm (range: 216–386 mm) [19].

Conclusions

OHSS can be considered as a classic model of IAH syndrome, where IAP is an important diagnostic marker associated with the severity of OHSS. In the present study assessing the level of IAP in 76 women with different degrees of OHSS, the median or the average value of IAP did not reach levels of IAH in cases of mild OHSS, while moderate OHSS was associated with IAH grade I, and severe OHSS was related to II–III IAH grade according to WSACS classification. In critical OHSS, the IAH level corresponds to ACS. The inclusion of IAP monitoring in the standard for the management of OHSS might be useful in specifying the severity and timely initiation of treatment, including methods to reduce IAP, prevent further organ dysfunction, and avoid the transition to a more severe stage of IAH and ACS.

Indicators of OV is related to OHSS severity and IAH level and is of particular importance in the initialization of OHSS.

AsI is simple and convenient for assessing the degree of ascites and can serve as an indirect indicator of the reserve volume of the abdominal cavity. In conjunction with clinical and laboratory data, ascites index and IAP values might be indicators for paracentesis.

Authors' Contributions AP and DM took part in patient recruitment for the study and conducted clinical trials. AP, CCB, DM, and EN designed the study. AP, CCB, DM, and EN took part in the analysis and interpretation of data and revision of the draft. AP, CCB, DM, and EN wrote the manuscript. CCB, AK, and ES revised critically for important intellectual content. All authors approved the final version of the manuscript. All authors had full access to all of the data in the study (including statistical reports and tables) and can take responsibility for the integrity of the data and accuracy of the data analysis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Informed consent was obtained from all the patients. The study was approved by the Ethics Committee of the Saratov State Medical University named after V. I. Razumovsky, Saratov, Russian Federation (IORG0004384, P.№7; 6 March 2018), and was performed in accordance with the Declaration of Helsinki II and the ICH Guidelines for Good Clinical Practice.

Abbreviations ACS, abdominal compartment syndrome; AsI, ascites index; IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure; IAV, intra-abdominal volume; OHSS, ovarian hyperstimulation syndrome; OV, ovarian volume; WASC , World Society for Abdominal Syndrome

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Table S1. ***Distribution of blood test results among severity classes of ovarian hyperstimulation syndrome***

Indicator	The severity of ovarian hyperstimulation syndrome				P value
	Mild (n = 25)	**Moderate** (n = 25)	**Severe** (n = 21)	**Critical** (n = 5)	
Hematocrit, %	37.0 [34.2 – 39.0]	42.0 [41.0 – 43.6]	49.4 [46.4 – 53.2]	56.1 [55.9 – 57.2]	$p<0.001$
White blood cell /ml	8 700 [6 700 – 11 800]	12 100 [10 900– 13 900]	19 000 [15 200– 23 900]	26 000 [25 800 – 26 300]	$p<0.001$
Platelets, $ml/^3$	247 [181 – 294]	192 [169 – 283]	320 [262 – 369]	396 [380 – 420]	$p<0.001$
Glucose, mmol/L	4.9 [4.1 – 5.2]	4.7 [4.1 – 5.2]	4.6 [3.9 – 5.2]	7.9 [7.2 – 8.1]	$p<0.005$
Albumin, g/L	41.3 [38.9 – 44.0]	37.5 [35.0 – 40.0]	30.6 [27.6 – 34.6]	21.4 [20.3 – 23.6]	$p<0.001$
Urea, mmol/L	4.3 [3.2 – 5.1]	5.2 [4.3 – 6.9]	6.4 [5.7 – 7.1]	7.8 [7.8 – 8.1]	$p<0.001$
Creatinine, mmol/L	78 [67 – 84]	72 [69 – 81]	84 [78 – 92]	134 [127 – 137]	$p<0.001$
Total bilirubin, mmol/L	11.7 [9.3 – 16.3]	12.7 [10.4 – 16.2)	15.2 [12.7 – 19.0]	19.4 [19.3 – 20.5]	$p<0.001$
Aspartate aminotransferase, U/L	21 [13 – 29]	26 [17 – 32]	44 [38 – 48]	61 [59 – 68]	$p<0.001$
Alanine aminotransferase, U/L	19 [14 – 24]	19 [15 – 25]	29 [26 – 34]	44 [43 – 49]	$p<0.001$
Potassium, mmol/L	4.1 [3.7 – 4.8]	4.3 [3.8 – 4.8]	5.0 [4.8 – 5.3]	5.3 [4.9 – 5.5]	$p<0.001$
Sodium, mmol/L	140 [137 – 143]	137 [136 – 140]	135 [134 – 141]	132 [131 – 133]	$p<0.001$
Fibrinogen, g/L	3.4 [2.8 – 3.9]	3.8 [3.2 – 4.2]	5.7 [4.9 – 6.3]	7.0 [6.7 – 7.1]	$p<0.001$

Data are presented as median [interquartile range]

Differences between groups were assessed with Kruskal-Wallis test

Table S2. ***Ovarian volume, ascites index and intra-abdominal pressure versus clinical severity of ovarian hyperstimulation syndrome***

Indicator	The severity of ovarian hyperstimulation syndrome				P value
	Mild (n = 25)	**Moderate** (n = 25)	**Severe** (n = 21)	**Critical** (n = 5)	
Ovarian volumes, ml	307 [132 – 392]	500 [441 – 561]	578 [533 – 611]	600 [487 – 704]	$p<0.001$
Ascites index, mm		197 [140 – 235]	285 [276 – 312]	320 [310 – 346]	$p<0.001$
Intra-abdominal pressure, mmHg	4.0 [3.0 – 6.5]	12.0 [11.0 – 13.0]	16.0 [14.5 – 18.0]	25.0 [24.0 – 27.0]	$p<0.001$

Data are presented as median [interquartile range]
Differences between groups were assessed with Kruskal-Wallis test

Article 5

ARE ANTHROPOMETRIC DATA A TOOL FOR DETERMINING THE SEVERITY OF OHSS? YES, IT COULD BE!

Petrenko AP, Castelo-Branco C, Marshalov DV, Kuligin AV, Shifman EM, Nesnova ES, Batsunova MO has been published in **BMC Women's Health**

All management guidelines of ovarian hyperstimulation syndrome (OHSS) recommend daily monitoring of women's body weight, waist circumference, and note that as rates increase, the OHSS severity also increases. However, the dynamics of abdominal size and its relationship with markers of OHSS severity have not been highlighted. The purpose of this study is to assess the usefulness of various anthropometric indicators for determining the degree of OHSS severity as well as paracentesis indications.

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- It is located in the first quartile according Citescore (Scopus) and in the beginning of the second quartile of the specialty of Obstetrics and Gynecology (Ranking position 40/83), according to the Journal Citation Reports 2020®.

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BMC Women's Health

RESEARCH ARTICLE Open Access

Are anthropometric data a tool for determining the severity of OHSS? Yes, it could be!

Aleksei Petrovich Petrenko[1,2,4], Camil Castelo-Branco[1*], Dimitry Vasilevich Marshalov[2,4], Alexander Valerievich Kuligin[2], Efim Munevich Shifman[3], Elena Sergeevna Nesnova[4,5] and Batsunova Mariia Olegovna[4]

Abstract

Background: All management guidelines of ovarian hyperstimulation syndrome (OHSS) recommend daily monitoring of women's body weight, waist circumference and note that as indicators increase, the severity OHSS also increases. However, the dynamics of abdominal size and its relationship with markers of OHSS severity have not been highlighted. The purpose of this study is to assess the usefulness of various anthropometric indicators for determining the degree of OHSS severity as well as paracentesis indications.

Methods: Observational study including 76 women complaining with OHSS. Clinical history, physical examination, laboratory tests, and ultrasound measurement of the ovarian volume (OV) and ascites index (AsI) were done in all cases. Intra-abdominal pressure (IAP) was assessed using an intravesical manometer. The anteroposterior diameter of the abdomen (APD) and transverse diameter of the abdomen (TS) were measured with a pelvimeter. The APD/TS ratio was calculated.

Results: The APD/TS ratio increased progressively and tended to be the highest in the most symptomatic stage of OHSS (Kruskal–Wallis test, $p<0.001$). The median APD/TS was significantly lower in patients with mild OHSS (0.55 [IQR, 0.44–0.64]) compared with severe OHSS (0.87 [IQR, 0.80–0.93]; $p<0.001$) or critical OHSS (1.04 [IQR, 1.04–1.13]; $p<0.001$). Similarly, the median APD/TS of the moderate OHSS group (0.65 [IQR, 0.61–0.70]) was significantly lower than that of the severe ($p<0.001$) and critical OHSS group ($p=0.001$). There was a strong positive correlation between APD/TS and IAP (Spearman's $r=0.886$, $p<0.01$). The APD/TS ratio showed a significant positive correlation with AsI (Spearman's $r=0.695$, $p<0.01$) and OV (Spearman's $r=0.622$, $p<0.01$). No significant differences were observed in age, height, weight, body mass index, hip circumference or waist circumference between moderate, severe and critical OHSS groups.

Conclusions: The APD/TS ratio is related to the severity of OHSS. Monitoring APD/TS dynamics could be a method of indirectly controlling intra-abdominal volume, compliance of the abdominal wall and IAP. In conjunction with clinical and laboratory data, APD/TS might be an indicator for paracentesis.

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Keywords: Ovarian hyperstimulation syndrome, Anthropometic indicators, Intra-abdominal pressure, Intra-abdominal hypertension, Ascites index, Compliance of the abdominal wall

Background

Ovarian hyperstimulation syndrome (OHSS) is a largely iatrogenic condition, associated with significant morbidity and even mortality of healthy women undergoing fertility treatment [1, 2]. Generally, OHSS is triggered by human chorionic gonadotropin (hCG) and it's mainly due to excessive ovarian secretion of vascular endothelial growth factor and other angiogenic factors, increasing vascular permeability and causing fluid leakage into the third space [3, 4]. Thus, OHSS is characterized by enlarged ovaries with hypovolemia and haemoconcentration, in more severe cases including ascites, hypercoagulation, renal failure and even multiple organ failure in the critical ones [2]. The main principles in moderate and severe OHSS treatment are correction of hypovolemia, electrolyte imbalance, hypoalbuminemia and paracentesis, if necessary [5].

Ascites progression and ovarian enlargement with OHSS leads to an increase in intra-abdominal pressure (IAP), and in severe and critical formsto the abdominal compartment syndrome (ACS) and associated severe organ dysfunction, which is the main factor of poor outcome among women with this syndrome [6, 7]. Our previous study revealed OHSS as a classic model of intra-abdominal hypertension (IAH) syndrome, where IAP is an important diagnostic marker, allied with the OHSS severity [8]. It has been proposed, there was provided to use the IAH level and ascites index (AsI), for paracentesis's indications in combination with clinical and laboratory data. The IAP measuring through a Foley catheter by using a pressure transducer is the gold standard [9], but, unfortunately, it has not yet become widespread in gynecological and obstetric practice. Finding a simpler and more convenient method for indirect controlling intra-abdominal volume (IAV), abdominal wall compliance (Cab) and IAP without the use independently of complex and expensive techniques would be useful for OHSS management.

All OHSS management guidelines recommend daily monitoring of women's body weight, waist circumference (WC) and note that as indicators increase, the severity of OHSS also increases [5, 10–12]. However, according to the literature data, the dynamics of abdominal size and its relationship with markers of OHSS severity have not been highlighted.

The purpose of this study is to assess the usefulness of various anthropometric indicators in determining degree of OHSS severity as well as indications for paracentesis.

Methods

Sample

A total of 76 infertile women who were in an in vitro fertilization program and presented OHSS were included in this study. Sample size was established based on the fact that according to the Ministry of Health of the Saratov Region, during the period from 2015 to 2019, 4800 cycles of ART were performed in all medical institutions of the region. Complications presented by various forms of OHSS requiring outpatient monitoring and hospitalization, were recorded in 95 cases (1.9%). Thus, using the statistical software to calculate the sample size with a 5% maximum acceptable error, 95% confidence level, we obtained a sample size of 76 women with OHSS. All of them were admitted into the gynaecological department of the city clinical hospital No.1 named after Yu.Ya. Gordeev (Saratov, Russian Federation). Anthropometrical, laboratory and clinical data were recorded in all included subjects (Additional file 1: Table S1, Additional file 2: Table S2 and Additional file 3: Table S3). The age range of the study participants was from 20 to 40 years old and the body mass index (BMI) was from 16.9 to 24.1 kg/m^2.

OHSS was classified according to the Royal College of Obstetricians & Gynaecologists guidelines [5]. Therefore, patients were allocated into four groups depending on the severity of OHSS: mild OHSS (group I, n=25), moderate OHSS (group II, n=25), severe OHSS (group III, n=21), and critical OHSS (group IV, n=5). Early-onset OHSS was defined when the syndrome was initiated during the first 9 days after trigger administration of hCG, and late OHSS was defined when the syndrome was initiated from 10 days after. The current study included 19 (25%) women with early OHSS and 57 (75%) women with late OHSS. The IAP was measured 4 [IQR, 3–5] days after hCG administration in case of early OHSS and 17 [IQR, 13–19] days after hCG triggering in case of late OHSS. The average length of stay for subjects with early OHSS was 10 [IQR, 7–12] days; the average length of a hospital stay for women with late OHSS was 9 [IQR, 7–11] days. All women admitted with the diagnosis of OHSS were considered for inclusion in the study. Those who voluntarily refused to participate were excluded.

Procedures

Anthropometrical and clinical data were recorded in all included subjects (Additional file 2: Table S2 and Additional file 3: Table S3). The anteroposterior diameter of the abdomen (APD) and transverse diameter of the

abdomen (TS) were measured with a pelvimeter. The APD was defined as the distance between the spine at the L_{3-4} level and the abdomen apex, then the pelvimeter branches were rotated in the same plane, set along the midaxillary lines, and after that, TS measurement was made. The APD/TS ratio was calculated.

BMI was evaluated by the Quetelet's equation, and in all cases blood and urine samples were obtained. Ovarian size and pelvic and abdominal free fluid were assessed by ultrasound (Accuvix XG [Samsung MEDISON Co. Ltd. Korea]) using 3.5 MHz sectoral sensors. The ovarian volume (OV) using the prolate ellipsoid formula [13] and the AsI [14] was measured as previously described [8]. Finally, the IAP was determined using a Foley catheter with a pressure transducer [9].

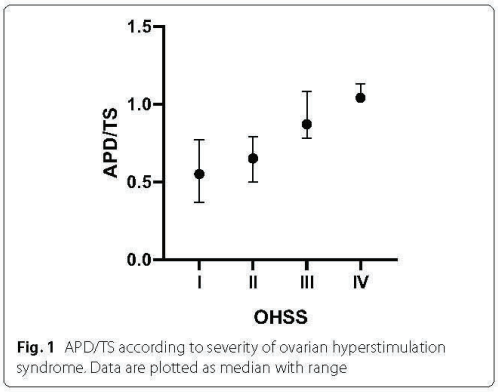

Fig. 1 APD/TS according to severity of ovarian hyperstimulation syndrome. Data are plotted as median with range

Statistical analysis

The data were analysed using a personal computer-based software package (SPSS 26.0, SPSS Inc. Headquarters, 233 South Wacker Drive, 11th Floor, Chicago, IL 60606, USA). The Shapiro–Wilk test was used to determine the normal distribution of the sample. Data for non-normally distributed variables are given as the median [interquartile range]. Homogeneity of within-group variances was evaluated by Levene's test. The Kruskal–Wallis test was used to analyse differences between groups. Statistically significant results were followed by Mann–Whitney U-tests with Bonferroni adjustment to detect subgroup differences. Spearman's correlation coefficients were used to check the association between continuous variables. All probability tests were two-sided and a p-value of < 0.05 was considered significant.

Results

Anthropometrical data are given in Additional file 3: Table S3. The age range of the study participants was from 20 to 40 years old and the BMI was from 16.9 to 24.1 kg/m^2.

Significant differences between groups were observed regarding APD measurements ($p < 0.001$). The median APD of the mild OHSS group (16 [IQR, 15–19]) was found to be significantly lower than that of the severe (24 [IQR, 23–27], $p < 0.001$) and critical OHSS group (26 [IQR, 24–28], $p = 0.001$). Besides that, the median APD of the moderate OHSS group (19 [IQR, 17–24]) was significantly lower than that of the severe ($p < 0.005$) and critical OHSS group ($p < 0.05$). However, there was no significant difference in APD between mild and moderate or severe and critical OHSS groups ($p > 0.05$).

As expected, APD/TS increased progressively and tended to be the highest in the most symptomatic stage of OHSS ($p < 0.001$). Figure 1 represents the intergroup comparison of APD/TS. The median APD/TS was significantly lower in patients with mild OHSS (0.55 [IQR, 0.44–0.64]) compared with severe OHSS (0.87 [IQR, 0.80–0.93]; $p < 0.001$) or critical OHSS (1.04 [IQR, 1.04–1.13]; $p < 0.001$). Similarly, the median APD/TS of the moderate OHSS group (0.65 [IQR, 0.61–0.70]) was significantly lower than that of the severe ($p < 0.001$) and critical OHSS group ($p = 0.001$). There was no significant difference in APD/TS between mild and moderate or severe and critical OHSS groups ($p > 0.05$).

No significant differences were observed in age, height, weight, body mass index, hip circumference or waist circumference between moderate, severe and critical OHSS groups (Additional file 2: Table S2). There was also no significant difference between the early and late OHSS groups ($p > 0.05$).

Correlation analysis was used to identify whether the APD/TS was independently associated with other anthropometric indicators and IAP, AsI or OV. As anticipated, there was a strong positive correlation between APD/TS and IAP (Spearman's $r = 0.886$, $p < 0.01$; Fig. 2a). Besides that, APD/TS showed a significant positive correlation with AsI (Spearman's $r = 0.695$, $p < 0.01$; Fig. 2b) and OV (Spearman's $r = 0.622$, $p < 0.01$; Fig. 2c). No significant correlation was present between APD/TS and any of the other anthropometric indicators, except for a weak inverse correlation with WC (Spearman's $r = -0.24$, $p < 0.05$). A significant but weak inverse correlation was observed between APD/TS and the age (Spearman's $r = -0.285$, $p < 0.05$).

Discussion

In a previous study, we made an analogy between OHSS and IAH syndrome documenting the importance of dynamic monitoring of IAP, AsI and OV. All these

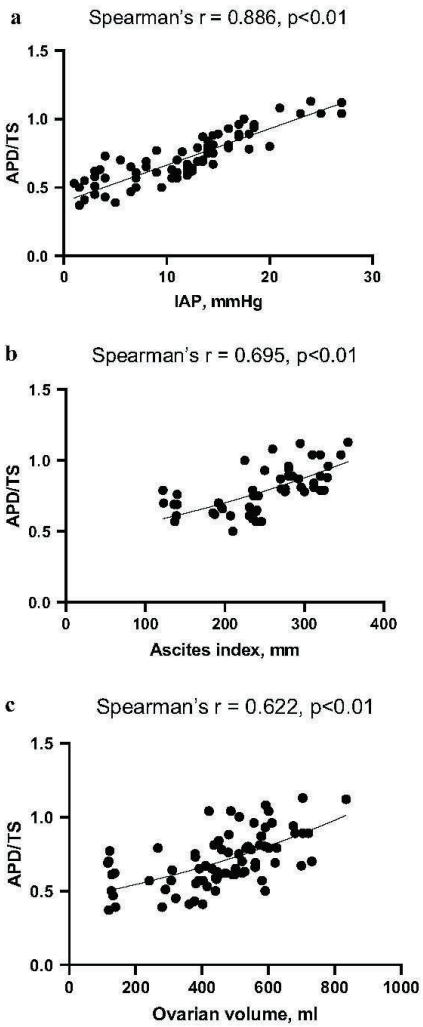

Fig. 2 Scatter plots of APD/TS related to intra-abdominal pressure (**a**), ascites index (**b**) and ovarian volumes (**c**)

parameters were significantly associated with the OHSS severity [8]. In the present research, we studied the women's anthropometric data and their relationship with OHSS severity.

All OHSS management guidelines emphasize the importance of daily monitoring of weight and WC in women and simply state the fact that the severity of OHSS increases with increasing these parameters [5, 10–12]. In our work, we did not observe significant differences in weight, BMI, HC or WC between moderate, severe and critical OHSS groups. Our data are consistent with those by Ma et al., who noted that increasing BMI is not a risk factor for OHSS severity [15]. Malbrain et al., when examining patients in intensive care, also stated that there was no significant correlation between abdominal circumference and IAP level [16].

It is a well-known that IAP is determined by two elements—the IAV and Cab [17]. The WC in women reflects approximate IAV, but not Cab and associated IAP. Women can have the same ascetic fluid amount, but different Cab, different possibilities for abdominal cavity accommodation and, as a result, different IAP. According to the World Society of Abdominal Compartment Syndrome (WSACS) experts, Cab plays a key role in understanding the negative effects of unadapted IAV on IAP and organ perfusion, although it is currently one of the most neglected parameters in critically ill patients [18]. Cab extension indicates a loss of abdominal wall elasticity, while a decrease in Cab means that the same change in IAV will result in a larger change in IAP.

Malbrain et al., in their fundamental work, studied the stages of changing in the abdominal shape in critically ill patients with IAH/ACS and revealed a change from an ellipse to a sphere with a maximum increase in IAP values. The authors described three phases of the ongoing processes: the reshaping, stretching, and pressurisation phases [19].

In the presented study, we obtained similar results. In the absence of significant intergroup differences in WC, the median APD in the moderate OHSS group was significantly lower than in the severe and critical OHSS group. Obviously, with the progression of ascites, APD increases most of all. The APD/TS ratio progressively increased and was highest at the most symptomatic stage of OHSS (Fig. 1). When the ratio APD/TS is approaching to 1, i.e. when the transverse and anteroposterior dimensions became equal, the abdomen took the sphere form with the transition from severe to critical OHSS. No significant difference in the APD/TS between mild and moderate OHSS can be explained by the fact that in moderate form there is a small amount of ascitic fluid with a sufficient elasticity reserve of the anterior abdominal wall and APD, as well as TS change insignificantly. Also, between severe and critical OHSS, there was no significant difference in the APD/TS. It can be due to the fact, that in severe form with exhaustion of abdominal stretching allowance, even a small addition of ascitic

fluid slightly changes both, APD and TS, but causes an exponential increase in IAP with the transition to critical OHSS. Correlation analysis also confirmed a significant positive correlation between APD/TS and OHSS severity markers, where the strongest positive correlation was between APD/TS and IAP.

It can be assumed that women with severe OHSS had an initially lower Cab compared with mild OHSS, and an increase in additional IAV with limited Cab led to a progressive IAP increase. Unfortunately, Cab measurement and estimation are difficult at the patient's bedside and can only be done in a case of change (removal or addition) in IAV [20]. This limitation also applies to IAV, which can be assessed by three-dimensional ultrasound, water-suppressed magnetic resonance imaging and computed tomography [19]. These are complex and expensive techniques which have not yet gained access to widespread clinical practice. Weak inverse correlation of APD/TS with WC seems illogical, although it can be explained by the fact that with increasing severity of OHSS, the median WC and BMI in the groups decreased, and the median Height increased (Additional file 2: Table S2). Thus, it can be stated that, asthenic type of constitution prevailed in the groups with severe and critical OHSS. The obtained results are consistent with the literature data, where asthenic habitus is indicated as one of the leading risk factors for the OHSS development [2, 10].

In a study assessing the IAV physiology during pregnancy, the authors confirm that the IAV capacity and the tensile properties of pregnant women's abdominal wall can be predicted by the dynamics of the anteroposterior and transverse abdominal diameters [21]. It should be pointed out that the current clinical guidelines represent pregnancy as a chronic compensated state of IAP, where the abdominal wall slowly stretches, its Cab gradually increases, and the pregnant woman has time to adapt to slowly increasing IAP levels [22]. Whereas OHSS is a dynamic condition, a rapid increase in volume and/or pressure exceeds Cab, because there is no time for tissue adaptation and moderate OHSS can progress to severe OHSS within a few hours [6]. Many authors confirm that in such cases, paracentesis is the single most important treatment modality for life-threatening OHSS which isn't controlled by medical therapy [23–26]. Having the absence of the ability to measure IAP and Cab, the dynamics of the APD/TS ratio can be a surrogate indicator of the IAH degree, IAV increase, reserve capabilities of the abdominal wall's extensibility and can help in establishing indications for timely performed paracentesis.

Conclusions

The APD/TS ratio and its dynamics are important markers of OHSS severity. The APD/TS ratio increases progressively, reaching the highest values in the most symptomatic stage of OHSS.

IAP showed the strongest positive correlation with the APD/TS ratio; however, significant correlations were also found between APD/TS and AsI and OV.

When the ratio APD/TS is approaching to 1, and the anteroposterior and transverse abdominal dimensions become equal, the abdomen changes from an ellipse to a sphere, the reserve of abdominal wall stretching is depleted, and IAP exponential growth is observed with the transition from severe to critical OHSS. The APD/TS monitoring can be a method of indirectly controlling IAP, Cab and IAV reserve, without using complex and expensive techniques. The inclusion of APD/TS monitoring in the standard for the management of OHSS might be useful in specifying the severity and timely initiation of treatment, including methods to reduce IAP, prevent further organ dysfunction, and avoid the transition to a more severe stage of IAH and ACS. Finally, in the absence of IAP monitoring capabilities, the APD/TS ratio in conjunction with clinical and laboratory data might be an additional tool for indication for paracentesis.

Abbreviations

ACS: Abdominal compartment syndrome; APD: Anteroposterior diameter of the abdomen; AsI: Ascites index; Cab: Compliance of the abdominal wall; IAH: Intra-abdominal hypertension; IAP: Intra-abdominal pressure; IAV: Intra-abdominal volume; OHSS: Ovarian hyperstimulation syndrome; OV: Ovarian volume; TS: Transverse diameter of the abdomen.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-022-01701-5.

Additional file 1: Table S1. Baseline patients' characteristics.

Additional file 2: Table S2. Clinical and laboratory data according to the severity of ovarian hyperstimulation syndrome.

Additional file 3: Table S3. Anthropometric markers according to the degree of severity of the ovarian hyperstimulation syndrome.

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Author contributions

AP, DM and MB took part in patient recruitment for the study and conducted clinical trials. AP, CCB, DM, and EN designed the study. AP, CCB, DM, and EN took part in the analysis and interpretation of data and revision of the draft. AP, CCB, DM, and EN wrote the manuscript. CCB, AK, and ES revised critically for important intellectual content. All authors approved the final version of the manuscript. All authors had full access to all of the data in the study (including statistical reports and tables) and can take responsibility for the integrity of the

data and accuracy of the data analysis. All authors read and approved the final manuscript.

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Availability of data and materials
The study was registered at the ISRCTN registry; identifier: ISRCTN66235250, http://www.isrctn.com/ISRCTN66235250 and https://doi.org/10.1186/ISRCTN66235250; Data are available at: Castelo-Branco, Camil (2021), "Severity Markers in Women with Ovarian Hyperstimulation Syndrome", Mendeley Data, V1, https://doi.org/10.17632/ryhtps673s.1.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from all the patients. The study was approved by the Ethics Committee of the Saratov State Medical University named after V. I. Razumovsky, Saratov, Russian Federation (IORG0004384, P.№7; 6 March 2018) and was performed in accordance with the Declaration of Helsinki II and the ICH Guidelines for Good Clinical Practice.

Consent for publication
Not applicable.

Competing interests
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Table S3. *General patient characteristics*

Total number of patients	76
Age, years	28 [IQR, 22–32]
Long protocol with GnRH-a, N (%)	11 (14)
Short protocol with GnRH-a, N (%)	6 (8)
Protocol with GnRH-ant, N (%)	59 (78)
PCOS history, N (%)	18 (24)
Oligomenorrhea, N (%)	25 (31)
Pregnancy, N (%)	73 (95)
Hospital stay, days	8 [IQR, 4–13]
Primary/secondary infertility, N (%)	49 (64)/27 (36)
Time between LMP and symptoms, days	26 [IQR, 14–30]
Mild OHSS, N (%)	25 (33)
Moderate OHSS, N (%)	25 (33)
Severe OHSS, N (%)	21 (28)
Critical OHSS, N (%)	5 (6)

Data are presented as median [interquartile range]. GnRH-a=gonadotropin-releasing hormone agonist; GnRH-ant=gonadotropin-releasing hormone antagonist; N=number of patients; PCOS=polycystic ovary syndrome; LMH=last menstrual period.

Table S4. *Clinical and laboratory data according to the severity of ovarian hyperstimulation syndrome*

Indicator	The severity of ovarian hyperstimulation syndrome				P value
	Mild (n = 25)	**Moderate** (n = 25)	**Severe** (n = 21)	**Critical** (n = 5)	
Clinical parameters					
Intra-abdominal pressure (IAP), mmHg	4.0 [3.0 – 6.5]	12.0 [11.0 – 13.0]	16.0 [14.5 – 18.0]	25.0 [24.0 – 27.0]	p<0.001
Ascites index (AsI), mm		197 [140 – 235]	285 [276 – 312]	320 [310 – 346]	p<0.001
Ovarian volumes (OV), ml	307 [132 – 392]	500 [441 – 561]	578 [533 – 611]	600 [487 – 704]	p<0.001
Blood cells & coagulation					
Hematocrit, %	37.0 [34.2 – 39.0]	42.0 [41.0 – 43.6]	49.4 [46.4 – 53.2]	56.1 [55.9 – 57.2]	p<0.001
White blood cell /ml	8 700 [6 700 – 11 800]	12 100 [10 900– 13 900]	19 000 [15 200– 23 900]	26 000 [25 800 – 26 300]	p<0.001
Platelets, ml/^{3}	247 [181 – 294]	192 [169 – 283]	320 [262 – 369]	396 [380 – 420]	p<0.001
Fibrinogen, g/L	3.4 [2.8 – 3.9]	3.8 [3.2 – 4.2]	5.7 [4.9 – 6.3]	7.0 [6.7 – 7.1]	p<0.001
Basic metabolic panel					
Glucose, mmol/L	4.9 [4.1 – 5.2]	4.7 [4.1 – 5.2]	4.6 [3.9 – 5.2]	7.9 [7.2 – 8.1]	p<0.005
Albumin, g/L	41.3 [38.9 – 44.0]	37.5 [35.0 – 40.0]	30.6 [27.6 – 34.6]	21.4 [20.3 – 23.6]	p<0.001
Urea, mmol/L	4.3 [3.2 – 5.1]	5.2 [4.3 – 6.9]	6.4 [5.7 – 7.1]	7.8 [7.8 – 8.1]	p<0.001
Creatinine, mmol/L	78 [67 – 84]	72 [69 – 81]	84 [78 – 92]	134 [127 – 137]	p<0.001
Total bilirubin, mmol/L	11.7 [9.3 – 16.3]	12.7 [10.4 – 16.2)	15.2 [12.7 – 19.0]	19.4 [19.3 – 20.5]	p<0.001
Aspartate aminotransferase, U/L	21 [13 – 29]	26 [17 – 32]	44 [38 – 48]	61 [59 – 68]	p<0.001
Alanine aminotransferase, U/L	19 [14 – 24]	19 [15 – 25]	29 [26 – 34]	44 [43 – 49]	p<0.001
Potassium, mmol/L	4.1 [3.7 – 4.8]	4.3 [3.8 – 4.8]	5.0 [4.8 – 5.3]	5.3 [4.9 – 5.5]	p<0.001
Sodium, mmol/L	140 [137 – 143]	137 [136 – 140]	135 [134 – 141]	132 [131 – 133]	p<0.001

Data are presented as median [interquartile range]. Differences between groups were assessed with Kruskal-Wallis test.

Table S5. *Anthropometric markers according to the degree of severity of the ovarian hyperstimulation syndrome*

Indicator	**The severity of ovarian hyperstimulation syndrome**				**P value**
	Mild (n = 25)	**Moderate** (n = 25)	**Severe** (n = 21)	**Critical** (n = 5)	
Height, cm	167 [162 – 169]	165 [162 – 173]	165 [161 – 168]	174 [169 – 176]	Ns
Weight, kg	57.0 [52.0 – 60.0]	56.0 [53.0 – 63.5]	54.0 [52.0 – 58.0]	53.4 [53.0 – 58.6]	Ns
Body mass index (BMI)	20.7 [19.4 – 22.1]	20.6 [20.2 – 21.2]	20.3 [20.1 – 20.8]	17.6 [17.2 – 20.6]	Ns
Hip circumference (HC), cm	95 [91 – 98]	95 [92 – 97]	94 [89 – 97]	94 [89 – 96]	Ns
Waist circumference (WC), cm	89 [85 – 93]	87 [83 – 92]	86 [84 – 87]	84 [83 – 86]	Ns
Anteroposterior diameter of the abdomen (APD), cm	16 [15 – 19]	19 [16 – 24]	24 [23 – 27]	26 [24 – 28]	$p<0.001$
Transverse diameter of the abdomen (TS), cm	32 [26 – 36]	28 [24 – 36]	28 [25 – 30]	23 [23 – 26]	$p<0.01$
APD/TS	0.55 [0.44 – 0.64]	0.65 [0.61 – 0.70)	0.87 [0.80 – 0.93]	1.04 [1.04 – 1.13]	$p<0.001$

Data are presented as median [interquartile range]. Differences between groups were assessed with Kruskal-Wallis test. ns=no significant difference.

Discussion

The pathophysiology and accompanying clinical presentation of OHSS are almost identical to IAH syndrome, consistent with a role of increased IAP in OHSS. The IAH consists of a clinical triad [15]. The first component is respiratory compromise, as increased IAP elevates the diaphragm, thus affecting breathing. This is observed in OHSS, as many women complain of dyspnea and pleural effusions can occur. The second component of the IAH triad involves decreased venous return, as increased pressure compresses the inferior vena cava, impeding blood return to heart. The last component of the IAH triad is intestinal failure due to compression of internal organs, which can lead to decreased appetite and then nausea/vomiting as seen in OHSS. Beyond this described triad there are effects on renal, liver, and hematologic parameters that are common to both syndromes. Specific effects of increased IAP documented in IAH and ACS are summarized in Figures 1, 2 (Article 1).

By definition an increased IAP includes effects of the volume of the organs and viscera and the presence of fluid or space-occupying lesions within the cavity [42], which includes IAP increases in OHSS as the ovaries enlarge and ascitic fluid accumulates.

There are scant data on IAP levels in women with OHSS and most with small sample size [22,30-32,35,81]. Just in three case reports of severe OHSS, the authors recorded IAP numbers meeting ACS criteria [22,32,35]. It is to note the study by Maslovitz S. et al. including 19 patients, which shown that an average IAP of 17.5 ± 1.24 cm H2O is related to various symptoms, including decreased respiratory function, intense ascites, and oliguria [81].

In the present study assessing the level of IAP in 76 women with different degrees of OHSS, the median value of IAP did not reach levels of IAH in cases of mild OHSS, while moderate OHSS was associated with IAH grade I, and severe OHSS was related to II–III IAH grade according to WSACS classification. The relationship between IAP and OHSS severity is highly significant. The higher the IAP, the greater the severity.

Mild OHSS is related to a slight increase in IAP. In moderate OHSS, ascitic fluid accumulates and the ovaries continue to grow, but the abdominal cavity still adapts and IAP grows moderately. When transition to severe OHSS occurs, the reserve volume of the abdominal cavity is close to minimum values and the extensibility of the anterior abdominal wall is depleted, which results in a linear rapid increase in IAP.

Lastly, in critical OHSS, with the addition of a minimum amount of liquid, an explosive increase in IAP is observed. In critical OHSS, IAP values exceed 25 mmHg, and an explicit ACS develops with rapid progression to multiple organ failure. Our data are consistent with those by Shay S et al., who also noted the nonlinearity of the increase in IAP in patients with chronic dialysis [82].

Indications for paracentesis according to the guidelines of the RCOG [25] include (a) severe abdominal distension and abdominal pain secondary to ascites, (b) shortness of breath and respiratory compromise secondary to ascites and increased intraabdominal pressure, and (c) oliguria despite adequate volume replacement, secondary to increased abdominal pressure causing reduced renal perfusion. It is to note that in this guideline, IAP is mentioned in two of the three indications for paracentesis; however, there are no recommendations for monitoring it. Based on this fact, it can be ensured that in many cases of severe and critical OHSS, the ACS was underdiagnosed because routine IAP measurements are usually ruled out by many departments of gynaecology and ICUs and paracentesis is performed in patients with life-threatening conditions, that is, with already developed severe multiple organ dysfunction.

Current evidence directly associates the progressive increase in ovarian volumes (OV) with the severity of OHSS. Abbara and colleagues found that no patient with a mean OV < 100 ml was diagnosed with moderate to severe OHSS, whereas 16% of patients with OV between 101 and 200 ml and 56%of patients with OV > 200 ml were diagnosed with this condition [26].

OV was larger in patients with more symptomatic OHSS and in patients with increased ascitic volume. Our data confirms the relationship between OHSS severity and IAP with OV values: larger OV is associated with more severe OHSS and higher IAP. Nevertheless, it should be noted that the maximum increase in OV is observed between groups I and II, and as the OHSS severity increases, OV growth slows down, which indicates the significance of the increase in OV in the initialization of the OHSS. These findings are consistent with published data on the pathogenesis of OHSS as a result from the release of vasoactive substances from the ovary, such as VEGF and vascular permeability factor, due to excessive stimulation ovaries after the start of egg maturation during in vitro fertilization (IVF) treatment.

This leads to an increase in the permeability of capillaries and the movement of fluid from the intravascular compartment into the third space of the body [11,21]. Tense ascites and accompanying IAH in OHSS are well known facts [15,33,34]. Diagnosis of ascites based on complaints, physical methods, or ultrasound investigation is not problematic, but quantitative assessment of its amount is a difficult task. Physical methods of ascites monitoring used to date include sequential measurements of bodyweight, abdominal circumference, and determination of the protrusion index; however, such methods are often inaccurate and based on subjective interpretation. The indicator-dilution technique may be used for calculating the ascites volume, but it carries a risk of infection, bowel perforation, or haemorrhage [83]. Computed tomography enables to use 3D-rendering method for calculating the volume of ascites and allows to get the most reliable data, but this is an expensive method that requires an appropriate equipment [84]. From a clinical point of view, there is no need to know the exact amount of fluid in the abdominal cavity; what is important is to promptly establish indications for paracentesis in order to prevent further organ dysfunction and avoid the transition to a more severe stage of IAH and ACS.

In our study, we determined ascites index (AsI) by ultrasound, which is a simple and quick method to assess the degree of ascites. As Fig. 1 (Article 5) shows, there is a large increase in AsI indices between groups II and III. The abdominal cavity can still adapt to a certain amount of ascitic fluid. Then the reserve volume of the abdominal cavity and the extensibility of the anterior abdominal wall are depleted, and with a slight increase in AsI, a transition to critical OHSS with a progressive increase in IAH is visible. On the other hand, the higher IAP and AsI values before paracentesis, the stronger their decrease after drainage. Thus, the AsI can be considered an indirect indicator of the reserve volume of the abdominal cavity, that is, the volume that can be added to the basic IAV without the development of systemic dysfunctions associated with the growth of IAP.

In severe OHSS, when in most cases there are indications for paracentesis, the average AsI was 285 mm (276–312 mm). Our data is consistent with those from the study by Szkodziak P et al., who concluded that women with severe OHSS required decompressive paracentesis when median AsI was above 290 mm (range: 216–386 mm) [85].

In the present research, we studied the women's anthropometric data and their relationship with OHSS severity.

All OHSS management guidelines emphasize the importance of daily monitoring of weight and waist circumference (WC) in women and simply state the fact that the severity of OHSS increases with increasing these parameters [9,25,62,64]. In our work, we did not obtain significant differences were in weight, body mass index (BMI), hip circumference (HC) or WC between moderate, severe and critical OHSS groups. Our data are consistent with those by Ma T. et al., who noted that increasing BMI is not a risk factor for OHSS severity [11]. Malbrain M.L. et al., when examining patients in intensive care, also stated that there was no significant correlation between abdominal circumference and IAP level [86].

It is a well-known that IAP is determined by two elements – the intra-abdominal volume (IAV) and abdominal wall compliance (Cab) [39]. The WC in women

reflects approximate IAV, but not Cab and associated IAP. Women can have the same ascetic fluid amount, but different Cab, different possibilities for abdominal cavity accommodation and, as a result, different IAP. According to the WSACS experts, Cab plays a key role in understanding the negative effects of unadopted IAV on IAP and organ perfusion, although it is currently one of the most neglected parameters in critically ill patients [48]. Cab extension indicates a loss of abdominal wall elasticity, while a decrease in Cab means that the same change in IAV will result in a larger change in IAP.

Malbrain M.L. et al., in their fundamental work, studied the stages of changing in the abdominal shape in critically ill patients with IAH/ACS and revealed a change from an ellipse to a sphere with a maximum increase in IAP values. The authors described three phases of the ongoing processes: the reshaping, stretching, and pressurization phases [47].

In the presented study, we obtained similar results. In the absence of significant intergroup differences in WC, the median anteroposterior diameter of the abdomen (APD) in the moderate OHSS group was significantly lower than in the severe and critical OHSS group. Obviously, with the progression of ascites, APD increases most of all. The APD/TS ratio progressively increased and was highest at the most symptomatic stage of OHSS. When the ratio APD/TS is approaching to 1, i.e. when the transverse and anteroposterior dimensions became equal, the abdomen took the sphere form with the transition from severe to critical OHSS. No significant difference in the APD/TS between mild and moderate OHSS can be explained by the fact that in moderate form there is a small amount of ascitic fluid with a sufficient elasticity reserve of the anterior abdominal wall and APD, as well as transverse diameter of the abdomen (TS) change insignificantly. Also, between severe and critical OHSS, there was no significant difference in the APD/TS. It can be due to the fact, that in severe form with exhaustion of abdominal stretching allowance, even a small addition of ascitic fluid slightly changes both, APD and TS, but causes an exponential increase in IAP with the transition to critical OHSS.

No significant difference in the APD/TS between mild to moderate or severe to critical OHSS forms can be explained by the fact that moderate form has only small amount of ascites, while the severe form with exhaustion of abdominal stretching allowance, even with a slight addition of ascitic fluid enters the critical OHSS. Correlation analysis also confirmed a significant positive correlation between APD/TS and OHSS severity markers, where the strongest positive correlation was between APD/TS and IAP.

It can be assumed that women with severe OHSS had an initially lower Cab compared with mild OHSS, and an increase in additional IAV with limited Cab led to a progressive IAP increase. Unfortunately, Cab measurement and estimation are difficult at the patient's bedside and can only be done in a case of change (removal or addition) in IAV [49]. This limitation also applies to IAV, which can be assessed by three-dimensional ultrasound, water-suppressed magnetic resonance imaging and computed tomography [47]. These are complex and expensive techniques which have not yet gained access to widespread clinical practice. Weak inverse correlation of APD/TS with WC seems illogical, although it can be explained by the fact that with increasing severity of OHSS, the median WC and BMI in the groups decreased, and the median Height increased (Table S4). Thus, it can be stated that, asthenic type of constitution prevailed in the groups with severe and critical OHSS. The obtained results are consistent with the literature data, where asthenic habitus is indicated as one of the leading risk factors for the OHSS development [9,14].

In a study assessing the IAV physiology during pregnancy, the authors confirm that the IAV capacity and the tensile properties of pregnant women's abdominal wall can be predicted by the dynamics of the anteroposterior and transverse abdominal diameters [50]. It should be pointed out that the current clinical guidelines represent pregnancy as a chronic compensated state of IAP, where the abdominal wall slowly stretches, its Cab gradually increases, and the pregnant woman has time to adapt to slowly increasing IAP levels [53]. Whereas OHSS is a

dynamic condition, a rapid increase in volume and/or pressure exceeds Cab, because there is no time for tissue adaptation and moderate OHSS can progress to severe OHSS within a few hours [15]. Many authors confirm that in such cases, paracentesis is the single most important treatment modality for life-threatening OHSS which isn't controlled by medical therapy [33,34,35,81]. Having the absence of the ability to measure IAP and Cab, the dynamics of the APD/TS ratio can be a surrogate indicator of the IAH degree, IAV increase, reserve capabilities of the abdominal wall's extensibility and can help in establishing indications for timely performed paracentesis.

Thaler et al. were the first to describe the benefits of paracentesis in patients with OHSS and reported significant clinical improvement after ascitic fluid removal [87]. After this procedure, patients with OHSS significantly improve renal blood flow and increase diuresis as well as decrease the intensity of pulmonary symptoms and reduce the severity of respiratory failure [88]. After evacuation of ascites in patients with OHSS, a decrease in hematocrit and leukocytosis is also observed [88]. Moreover, after paracentesis pregnant women showed an increase in uterine perfusion [89]. The positive dynamics after paracentesis in patients with OHSS, might be explained by the effect of the decrease in the IAP due to the removal of the fluid.

However, in most cases, a statistically significant decrease in IAP is only recorded when at least 2000 ml of the liquid was removed. Controversially, improvement in renal blood flow and urinary function occurred with the removal of much smaller volumes of fluid [81]. This result suggests that the effect of paracentesis depend not on the volume of the removed liquid, but on decompression as such.

One of the goals of OHSS treatment is to prevent the progression of the severity of the syndrome. The previously recommended criteria for paracentesis were complaints of shortness of breath, abdominal distention, abdominal pain, oliguria, and ineffective treatment. In its first edition, the «Management of ovarian hyperstimulation syndrome, Green-top guideline, @ 5» recommended paracentesis

when the increase in IAP higher than 20mmHg [90]. However, whether the OHSS is considered from the point of view of the IAH syndrome, then early decompression, even with a moderate form of OHSS when ascites is not expressed, may be probably justified. In recent years, a reassessment of the importance of IAH in the OHSS is in motion. In the «Ovarian Hyperstimulation Syndrome (OHSS). Diagnosis and Management. Guideline @ 9» [91], a recommendation on early decompression is performed, even in an outpatient basis. Moreover, it has been proved that culdocentesis avoid the progression of OHSS to severe forms [91]. In the latest edition of the guideline «The management of the ovarian hyperstimulation syndrome, Green-top guideline, @ 5» (2016), the specific values of IAP (20 mmHg), in which it is necessary to proceed to paracentesis, have been replaced by an abstract 'increase' in IAP, which indicates the possibility of development of organ dysfunction with lower values of IAP [25].

Obviously, the inclusion of IAP monitoring and indirect methods of its control, described in our study, could significantly improve OHSS management.

Conclusions

- The present study supports the hypothesis of the negative role of IAH in the development of severe forms of OHSS and its complicated outcomes.
- OHSS can be considered as a classic model of IAH syndrome, where IAP is an important diagnostic marker associated with the severity of OHSS.
- Moderate OHSS was associated with IAH grade I, and severe OHSS was related to II–III IAH grade according to WSACS classification. In critical OHSS, the IAH level corresponds to ACS.
- Indicators of OV is related to OHSS severity and IAH level and is of particular importance in the initialization of OHSS.
- AsI is simple and convenient for assessing the degree of ascites and can serve as an indirect indicator of the reserve volume of the abdominal cavity. In conjunction with clinical and laboratory data, ascites index and IAP values might be indicators for paracentesis.
- The APD/TS ratio and its dynamics are important markers of OHSS severity. The APD/TS ratio increases progressively, reaching the highest values in the most symptomatic stage of OHSS and showed the strongest positive correlation with IAP.
- The APD/TS monitoring can be a method of indirectly controlling IAP, Cab and IAV reserve, and an additional tool for indication for paracentesis.
- Early intervention with culdocentesis or paracentesis prevents the progression of OHSS, does not allow reaching critical IAP and associated complications.
- The inclusion of IAP monitoring in the standard for the management of OHSS might be useful in specifying the severity and timely initiation of treatment, including methods to reduce IAP, prevent further organ dysfunction, and avoid the transition to a more severe stage of IAH and ACS.

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