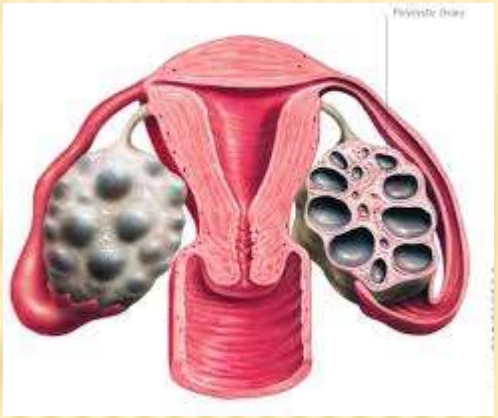
VAISINGUMO KLINIKA

CLINICAL ASPECTS OF OVARIAN HYPERSTIMULATION SYNDROME



Assoc. Prof. Egle Drejeriene
"Vaisingumo klinika"
Lithuanian University of Health Sciences
Medical Academy
Vilnius, 2014

OHSS – GENERAL DEFINITION (1)

- It is potentially life-threatening mostly iatrogenic complication of ovarian stimulation .
- A consequence of an exaggerated reponse to ovulation induction therapy.
- Iatrogenic OHSS occurs during ovarian stimulation with exogenous FSH, or rarely with clomiphene citrate. OHSS usually is dependent on the administration of hCG .

OHSS - GENERAL DEFINITION (2)

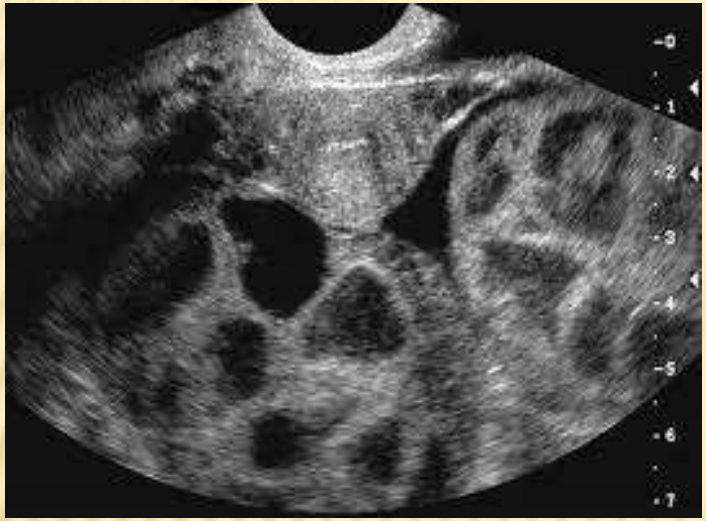
- OHSS is characterized by an increased size of ovaries due to multiple cysts, and by increase in the vascular permeability causing ascites, pleural effusion and sometimes even pericardial effusion.
- Severe forms are also accompanied by electrolyte disturbances and cardiopulmonary, hepatic, renal and hemodynamic disturbances associated with increased thromboembolic risk.
- The prevalence of severe forms – 0.5-5%.

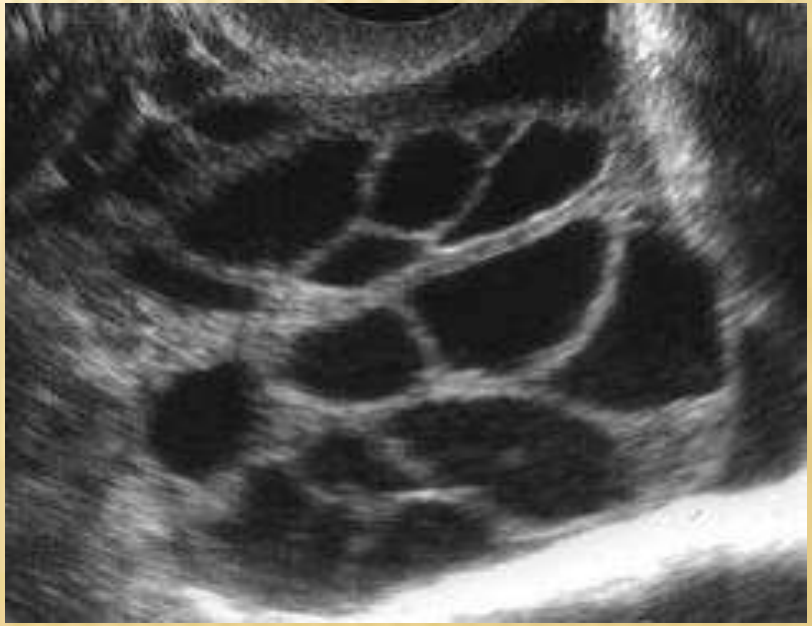
OHSS – PATHOPHYSIOLOGY (1)

- Massive enlargement of the ovaries with multiple follicular and thecaluteinic cysts, stromal oedema, cortical necrosis and the start of neovascularisation.

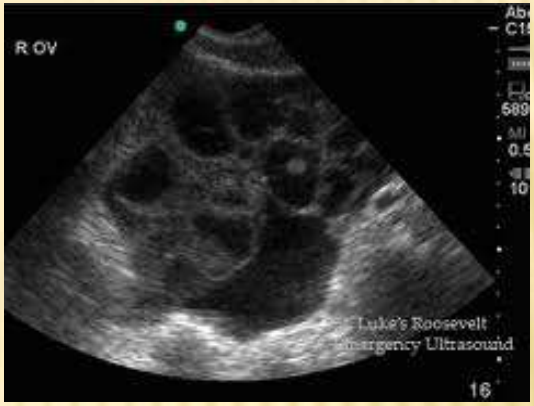
- The sudden redistribution of body fluids due to a significant increase in capillary permeability (fluid shift to the third space). This leads to the development of ascites and pleural (pericardial) effusion.

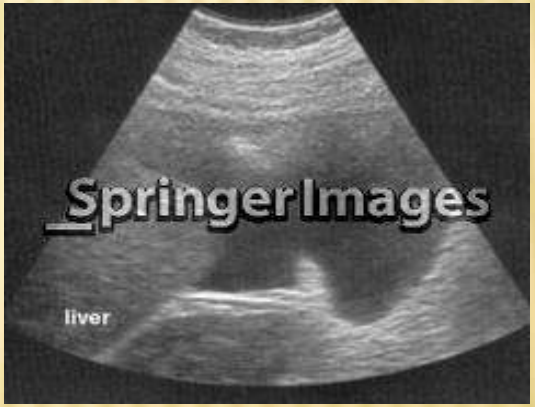
OHSS – US SCAN





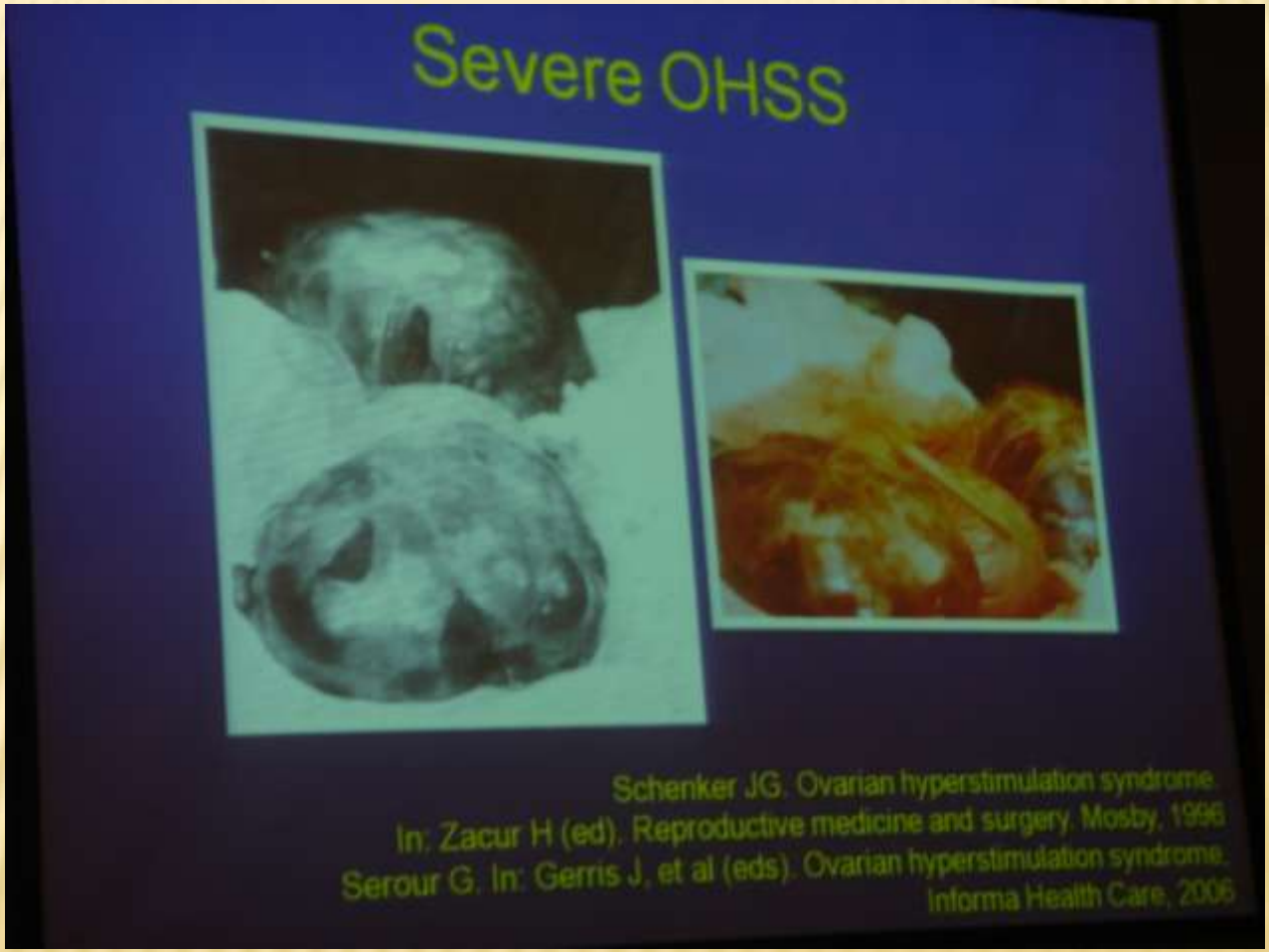
OHSS CLINICAL MANIFESTATION - ASCITES



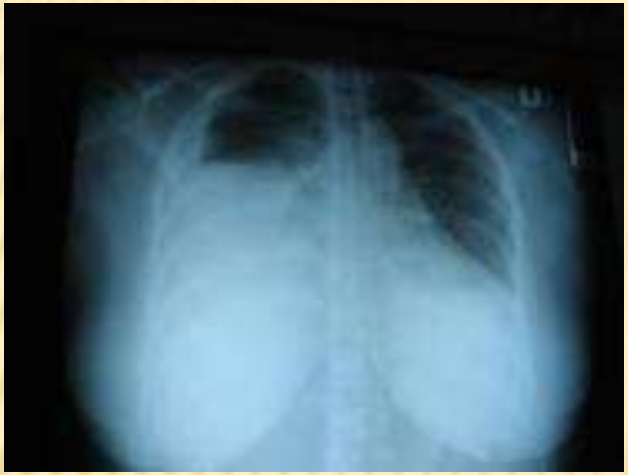


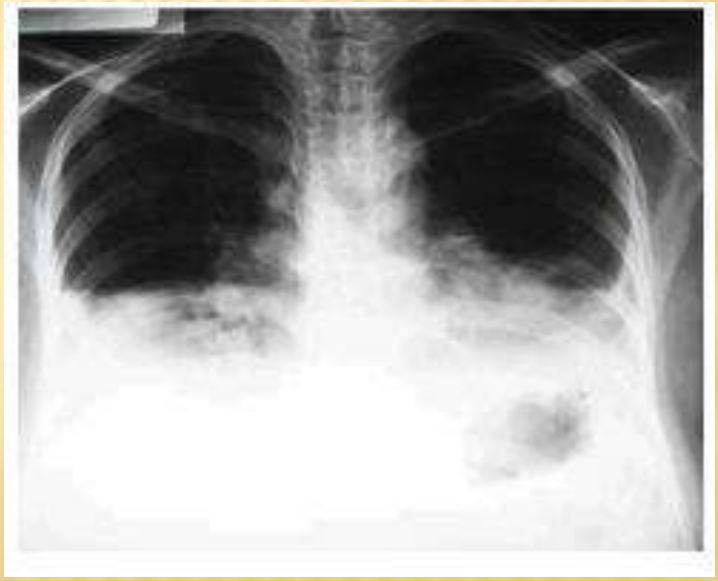
OHSS CLINICAL MANIFESTATION – ASCITES AND VULVAR OEDEMA

OHSS MANIFESTATION – MASSIVE ENLARGEMENT OF THE OVARIES



OHSS – PLEURAL EFFUSION





OHSS – PATHOPHYSIOLOGY (2)

- The main mediator of OHSS – VEGF. The balance of proangiogenic and antiangiogenic factors in the follicular fluid is important.
- Antiangiogenic factors reduce the risk of OHSS.

OHSS – PATHOPHYSIOLOGY (3)

- Pathophysiological cascade of OHSS:

  Neoangiogenesis⟶ increased capillar permeability in the ovaries and in the endothelium of other tissues⟶ redistribution of body fluids with abdominal, pleural and pericardial effusion ⟶ hemoconcentration⟶ decreased renal clearance⟶ oliguria / anuria⟶ increased blood viscosity⟶ coagulation disorders and increased thromboembolic / thrombotic complications.

  Decrease of albumin levels because of redistribution of the body fluids.

OHSS PATHOPHYSIOLOGY (4)

- Hemoconcentration leads to:

  ↑Ht, thrombocytosis, leukocytosis, elevated liver enzymes, ↑levels of urea and creatinin, hyperkalemia, acidosis.

Process is usually stabilized by drop of hCG level.

RISK FACTORS FOR OHSS (1)

- Primary:
  - **Polycystic ovary syndrome**
  - **Patients with some chracteristics of PCOS:**
    - High number of follicles in both ovaries at the quiescent state (≥10 4-10 mm in each ovary)
    - LH/FSH>2
    - ↑ androgens.
  - **History of OHSS**
  - Young patients*
  - Lean women*
  - Allergic predisposition *

Gerris J, De Sutter P. Ovarian hyperstimulation syndrome: summary and guidelines. In:Gerris J., Delvigne A., Olivennes F. (ed). Ovarian hyperstimulation syndrome. Informa Healthcare, 2006

RISK FACTORS FOR OHSS (2)

Secondary:

- Maximum serum estradiol 3000-4000 pg/ml:
  - No clear cut-off value
  - Relatively poor predictive power (max 73%)
  - OHSS may develop with lower E2 concentrations (rec FSH), E2 is not mediator of OHSS
  - The slope of the estradiol rise is the main risk factor and is of more importance than than the maximum level (PPV - 77%).

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RISK FACTORS FOR OHSS

- Secondary:
  - Number of follicles per ovary > 20-25:
    - No clear cut-off value (10-35)
    - Variation dependent upon operator and technique
  - Measurements of the absolute VGEF concentrations ar not useful for individual prediction.

Mathur et al. Serum vascular endolthelial growth factor levels are poorly predictive of subsequent ovarian hyperstimulation syndrome in highly responsive women undergoing assisted conception. Fertil. Steril 2002.

CLASSIFICATION OF OHSS (1)

- Early form- 3-7 days after hCG administration – elicited by hCG and is related to an exaggerated ovarian response to stimulation. The clinical course is more difficult.

- Late form- 12-17 days after hCG administration, mainly related to the secretion of placental hCG. The clinical course lighter but more prolonged.

CLASSIFICATION OF OHSS (2)

Mild	Moderate	Severe	Critical
Bloating	Vommiting	Massive ascites	Tense ascites
Nausea	Abdominal pain	Hydrothorax	Hypoxemia
Abdominal distension	US evidence of ascites	Hct > 45%	Percardial effusion
Ovaries ≤5 cm	Hct>41%	WBC > 15 000/mm^3	Hct > 55%
	WBC > 10 000/mm^3	Oliguria	WBC > 25 000/mm^3
		Creatinine 1-1,5 mg/dl	Oliguria or anuria
	Ovaries > 5 cm	Creatinine clearance ≥50 ml/min	Creatinine >1,5 mg/dl
		Hepatic dysfunction	Creatinine clearance < 50 ml/min
		Anasarca	Renal failure
		Ovaries variably enlarged	Thromboembolic phenomena
			ARDS
			Ovaries variably enlarged

Levine Z, Navot D. Modern classification of the ovarian hyperstimulation syndrom. In:Gerris J., Delvigne A., Olivennes F. (ed). Ovarian hyperstimulation syndrome. Informa Healthcare, 2006

PREVENTION OF OHSS (1)

- Primary:
  - Patients should be exposed to gonadotropins as little as possible (life-style changes (diet and exercises), oral ovulation induction, laparoscopic ovarian drilling)
  - The identification of women with thrombophilia, those with a family history of thromboembolism and women with antiphospholipid antibodies should ideally be performed before starting gonadotropin treatment.
  - The lowest possible dose of gonadotropins should be used.
  - All patients should be informed verbally and in writing about the possible risk.
  - In cases of high risk, prophylactic treatment with heparin has been proposed .

Gerris J, De Sutter P. Ovarian hyperstimulation syndrome: summary and guidelines. In:Gerris J., Delvigne A., Olivennes F. (ed). Ovarian hyperstimulation syndrome. Informa Healthcare, 2006

PREVENTION OF OHSS (2)

- **Secondary:**
  - Cycle cancellation.
  - Coasting (*Continuing gonadotropins at a serum estradiol level of >3000 pg/ml is considered not good clinical practice) (*COCHRANE 2011 – insufficient evidence).
  - Modification of the ovulation – triggering agent
    - Lower doses of hCG (data is lacking),
    - Administration of short -acting GnRh agonist (in antagonist cycles),
    - Exogenous LH (recLH).
  - Albumin administration during oocyte retrieval (COCHRANE 2002 – YES, COCHRANE 2011 – NO).
  - Hydroxyethil starch solution – (COCHRANE 2011 – YES for severe OHSS)
  - Cryopreservation of all embryos (COHRANE 2007 -evidence is insufficient to consider this approach as the standart treatment)
  - Luteal phase support without hCG.
  - IVM

PREVENTION OF OHSS (3)

- **Secondary** (miscellaneous techniques with insufficient data):
  - Metformin
  - Ovarian suppression (continued administration of GnRh-a)
  - Corticosteroids
  - Calcium infusion
  - Dopamine agonists (VEGF antagonist) (COCHRANE 2012 – YES (for moderate OHSS).

PREVENTION OF OHSS (4)

- The purpose – OHSS free clinic.
- The ideal protocol of ovarian stimulation for ART:

  Antagonist protocol + GhRh-a, freeze all policy, ET in natural cycle.

Clinical aspects of OHSS

Skaistė Jankauskienė, Tautvydas Jankauskas,
Eglė Drejerienė
Lithuanian University of Health Sciences
Medical Academy
Obs/Gyn Dept

OBJECTIVES

- To evaluate the clinical manifestation and the management of the patients with OHSS.

STUDY DESIGN

- Retrospective study of case records . Patients were managed in Obs/Gyn Dept. of university hospital of LUHS during the period 2006-2011.

- For statistical data SPSS 17 package was used.
- For statistical significance $p<0,05$ and r [-1;1] *(Spearman correlation)* were used.

RESULTS (1)

- **26** patients, **27** cases were analysed (one patient was managed twice).
- The mean age – **30,7** (4,4) (range 22-39) years old.

Results (2)

MEAN DURATION OF INFERTILITY 3,7 (1,7) YEARS (RANGE 2-9)

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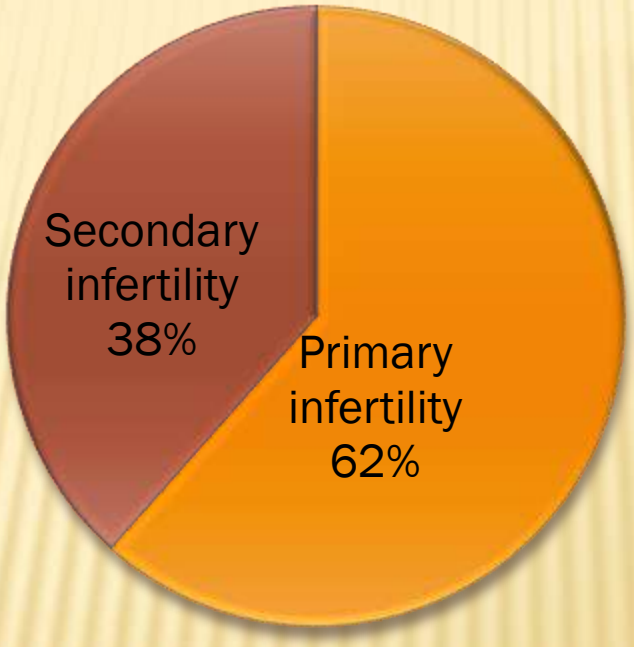
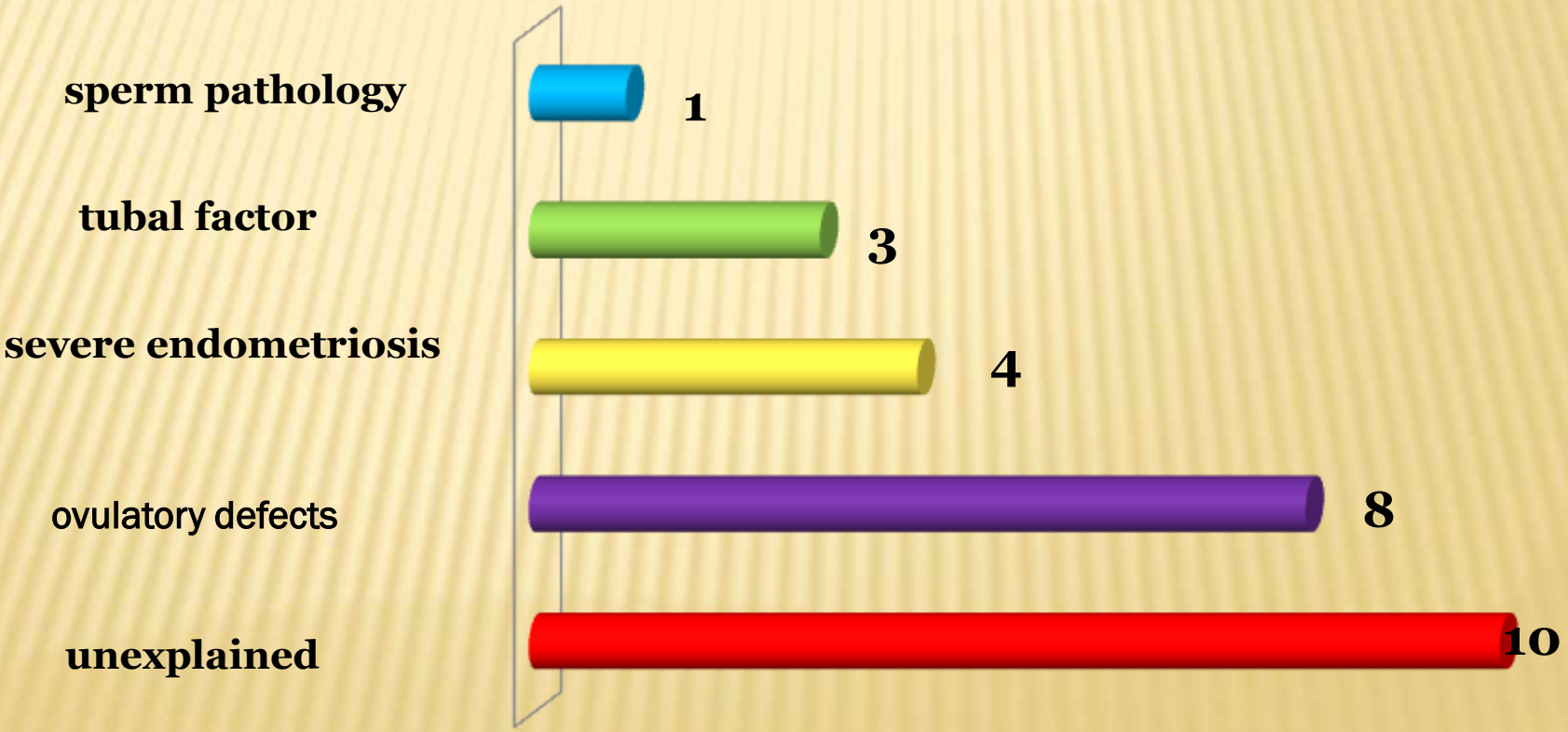


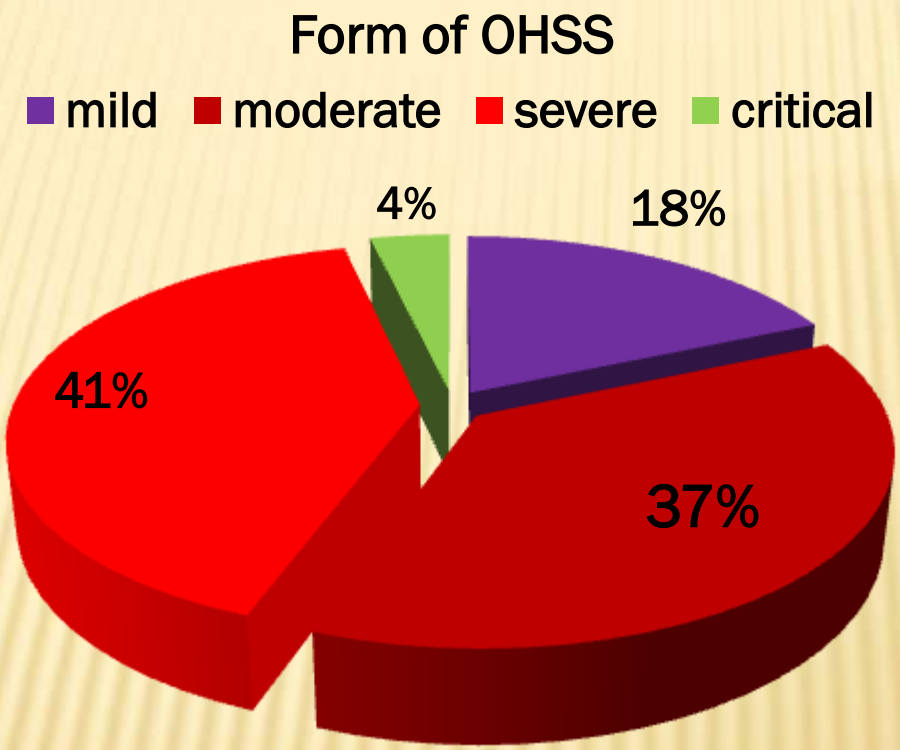
- The positive correlation between the age and duration of infertility r=0,5, p=0,03

RESULTS (3). CAUSES OF INFERTILITY.

11 patients with PCOS, 3 with history of OHSS

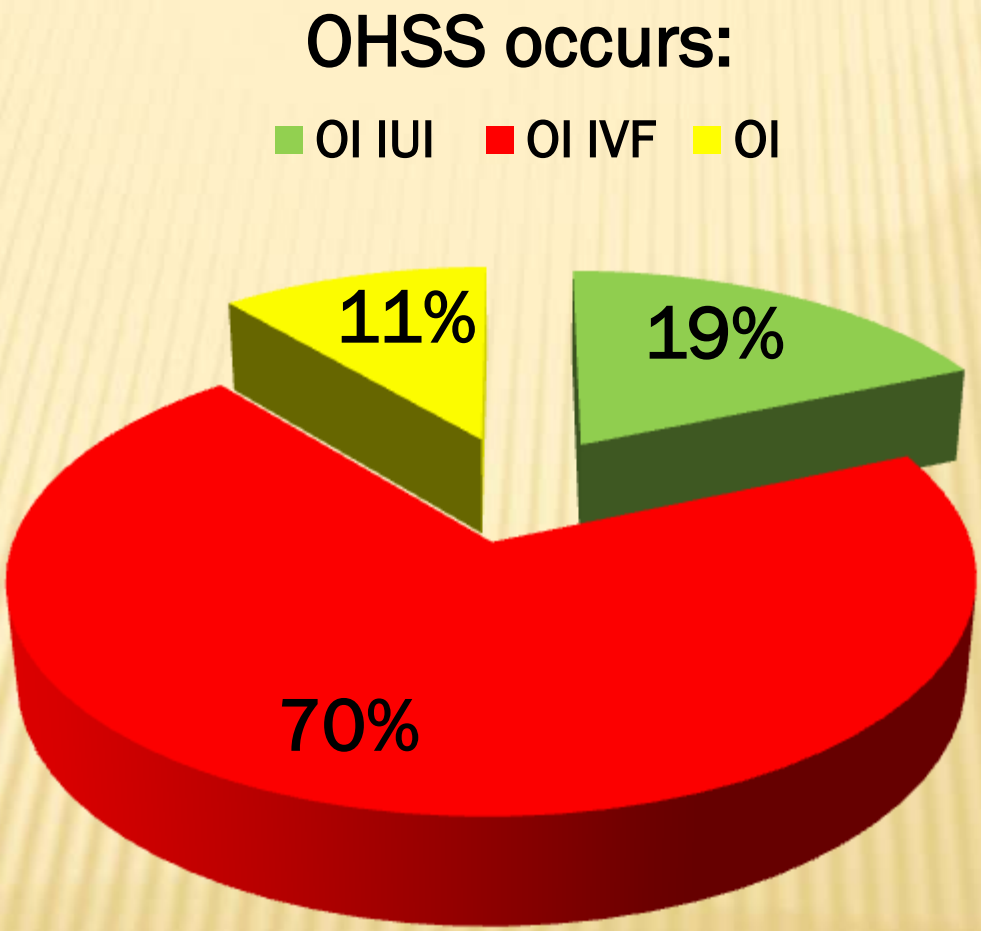


RESULTS (4)

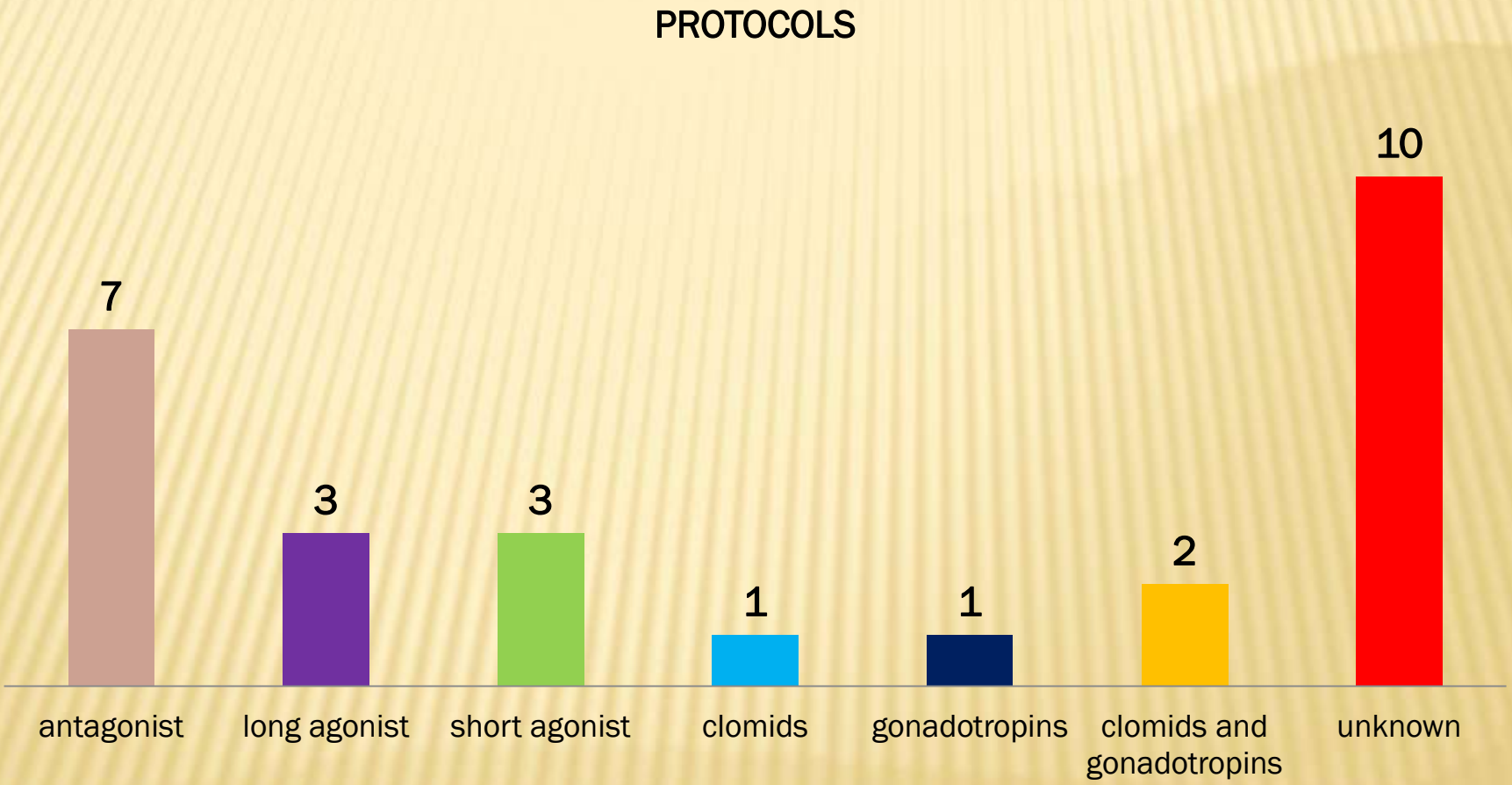


Negative correlation between stimulation protocol and OHSS form (p=0,2).

RESULTS (5)



RESULTS (6). OVULATION INDUCTION PROTOCOLS



RESULTS (7)

Complaints:

Abdominal distension100% (27)

Breathlessness 84% (23)

Nausea 72 % (20)

Vomiting 16% (4)

Diarrhoea 12% (3)

Fever 8% (2)

Weakness 92% (25)

Weight gain 72% (20)

Dysuria (lack of urine) 56% (14)

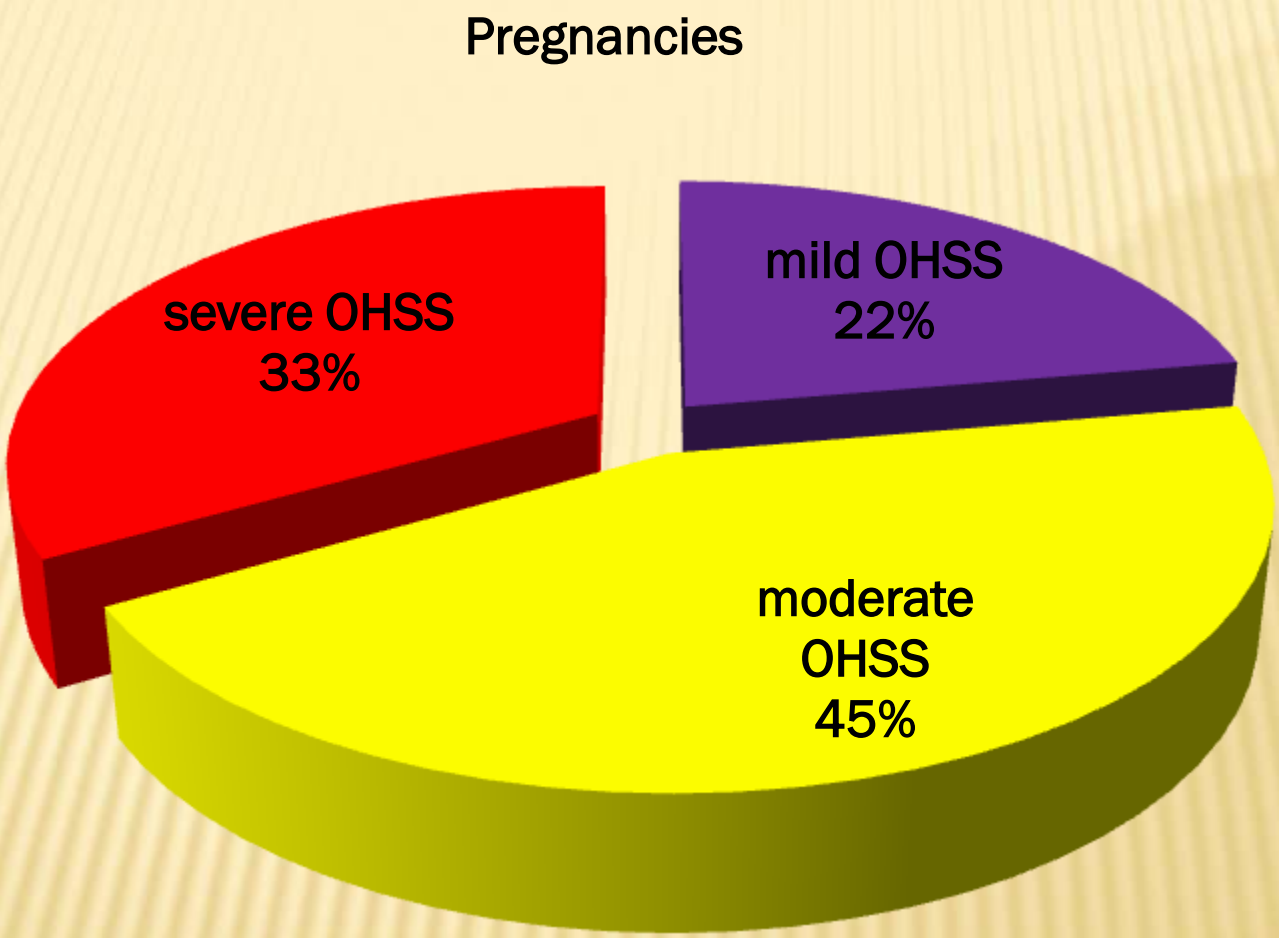
RESULTS (8). MANAGEMENT OF OHSS

- Fluid management – Riger‘s lactate and NaCl 0,9% solution depending on fluid balance.
- Plasma expanders – HES (hydroxyethyl starch).
- Albumin administration.
- Low-molecular-weight heparin.
- 11 - drainage of ascites, 2– drainage of hydrothorax, 1 - hemodialysis.
- **Invasive procedures mostly used for patients with severe and critical OHSS (p<0,00).**
- Mean duration of hospitalisation of patients with severe OHSS – 17,8 days, for patients with mild/moderate OHSS – 10 days.

RESULTS (9).

- 9 patients with OHSS conceived.
- 3 cases were multiple pregnancies.

RESULTS (10)



CONCLUSIONS

1. OHSS can develop with different regimens of OI. OHSS mostly occurs for the ART patients.
2. Patients with severe OHSS required longer hospitalisation.
3. Invasive procedures for OHSS management mostly are used for patients with severe and critical OHSS.
4. 1/3 of OHSS patients developed intrauterine pregnancies.

SUMMARY

- OHSS is potentially life-threatening complication which can disrupt the health of young and healthy woman.
- When ovulation induction with gonadotropins for ART is used the centers should follow local protocols for OHSS prevention.
- Patients with OHSS should be managed in the hospitals with possibilities of multidisciplinary team collaboration.