The ovarian hyperstimulation that truly matters: admissions, severity, and prevention strategies

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Background

Ovarian Hyperstimulation Syndrome (OHSS) is a serious complication of ovarian stimulation (OS) and a mandatory reportable complication of fertility treatment.[1] Moderate to severe forms pose significant risk to patients with hospitalisation, therapeutic interventions, and the potential for substantial morbidity and rarely mortality. The relevance of mild OHSS is questionable given its considerable overlap in clinical features with that of ovarian stimulation.

A more clinically relevant classification is required to better appreciate the impact of clinically significant disease.

Aims

- To formulate clinically relevant OHSS classification for inpatient settings and data collection/reporting
- Estimate OHSS prevalence requiring hospital admission in Victoria
- Determine the extent of OHSS preventability with clinical strategies

Methods

Conducted at a single tertiary centre estimated to treat 40% of OHSS cases in Victoria. All presentations included over a 5-year period from the 1st of January 2016 to the 31st of December 2021. Data were sourced from electronic and hardcopy medical records from the public hospital and affiliated private fertility service.

Data were collected included:

- Patient characteristics - age, BMI, length of stay, treating fertility centre
- Baseline indicators of ovarian reserve - antral follicle count and AMH
- Treatment regime - cycle type, duration of stimulation, FSH drug, FSH dosage and trigger
- Cycle outcomes - follicle number and oocytes retrieved
- Timing classification - early or late
- Clinical markers of disease severity - pain, nausea, vomiting, ultrasound evidence of ascites, ultrasound evidence of ovarian enlargement, electrolyte abnormalities including hyponatraemia and hyperkalaemia, hypoalbuminaemia, oliguria, ascites, hydrothorax, venous thromboembolism, acute respiratory distress syndrome, clinical intervention for ascites/hydrothorax, use of enoxaparin and administration of albumin.

Cases classified in accordance with the proposed inpatient classification system:

Severity	Mild	Moderate	Severe
Length of stay (days)	< 1	1 - 3	> 3
HCT > 0.50	x	1	1
Albumin < 30 g/L	x	1	1
Administration of Albumin	x	x	1
Paracentesis / drainage of hydrothorax	x	x	1
Venous thromboembolism (VTE)	x	x	1

Results

- 199/208 presentations were defined as true OHSS with further data relating to cycle protocols being available for 153 cases.

Demographics	Mild	Moderate	Severe	Total / mean	p value
Classification (n and %)	66 (33.2%)	38 (19.1%)	95 (47.7%)	199	N/A
Length of stay (days) (Mean and range)	0.77 (0 - 1)	2 (1 - 2)	5.2 (1-17)	3.1	N/A
Average Age (Mean and SD)	31.8 (4.24)	32.3(4.84)	32.7 (4.77)	32.3 (4.67)	0.48
BMI (Mean and SD)	25.4 (4.92)	25.7 (5.8)	26.5 (6.78)	26 (6.38)	0.65
Early onset/Late Onset (n and%)	48 (35%) 18 (29%)	26 (19%) 11 (17.7%)	61 (44.5%) 33 (53.2%)	137 (68.9%) 62 (31.2%)	0.57

Demographics	No. patients	Mild	Moderate	Severe	p value
Classification (n and % of total)	153	46 (30.1%)	34 (22.2%)	73 (47.7%)	N/A
Average age (Mean and SD)	153	31.3 (4.92)	32.15 (4.96)	32.89 (4.85)	0.27
Length of stimulation (days. Mean and SD)	153	9.8 (1.97)	10.9 (3.0)	10.35 (2.63)	0.17
BMI (Mean and SD)	129	25.32 (6.41)	25.21 (5.17)	26.67 (6.83)	0.47
AMH (Mean and SD)	104	44.61 (31.89)	48.91 (29.72)	49.1 (30.46)	0.79
Follicle number (Mean and SD)	153	23 (10.61)	26 (15.39)	22 (9.73)	0.22
Ooctyes retrieved (Mean and SD)	153	25 (11.59)	21 (8.66)	23 (9.53)	0.15
Daily FSH dose (Mean and SD)	153	175.7 (89.1)	162.2 (87.7)	181.8 (93.1)	0.58
Agonist trigger (number and percentage of total)	28 (18.3)	12 (7.8)	6 (3.9)	10 (6.5)	0.2
Early Onset/Late onset N and %	153 (105/48)	33 (31.4%) 13 (27.1%)	24 (22.9%) 10 (20.8%)	48 (45.7%) 25 (52.1%)	0.76

- Agonist trigger usage resulted in a statistically significant less severe disease (p=< 0.05)
- Agonist triggers combined (Lucrin/Decapaptyl) represented 15% of severe presentations compared to the hCG (Ovidrel/Pregnyl) representing 84.9%
- Agonist trigger use resulted in a higher number of follicles seen on ultrasound (34) compared to an antagonist trigger (21)
- Agonist trigger produced a higher number of oocytes (28 eggs) compared to hCG trigger (21 eggs)
- Between years 2018/2019 and 2020/2021 there were 255 admissions with significant OHSS to hospitals in Victoria [1,2,3]
- From 2018 – 2021 there were 39,658 stimulated cycles performed in Victoria, which equates to the risk of admission with OHSS of 0.64% [1,2,3]
- During 2018 – 2021 the RWH had a total of 103 admissions with OHSS, which represents approximately 40% of all admissions for OHSS in Victoria. OHSS requiring hospital admission is low, in the order of 6.5 cases per 1,000 oocyte collections
- One third of these patients are admitted for less than 24 hours, with no therapeutic interventions, which can be considered mild
- Two thirds of admissions are significant in nature where an admission for longer than 24 hours was required, or a specific therapeutic intervention was provided
- Therefore, the rate of clinically significant admissions in Victoria is in the range of 4-5 per 1,000 oocyte collections

Conclusions

- Clinically significant OHSS occurs in nearly half (47.4%) of all admissions over the 5 year study period
- There were no significant differences between factors recognised as predictive for high ovarian response which is in contradiction to the current literature
- Utilisation of an agonist trigger appears to reduce the incidence of severe OHSS
- Our data challenges the belief among clinicians that utilising an agonist trigger will virtually eliminate the incidence of clinically significant OHSS requiring hospitalisation

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