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Ovarian Hyperstimulation Syndrome and Myocardial Infarction: A Systematic Review

Mohammed Al-Sadawi[1], **Richi Chowdhury**[1], **Seline Asun**[1], **Justina Ray**[1], **Lina Soni**[1], **Gul Bahtiyar**[2], **Debora Ponse**[1], **Samy I McFarlane**[1,*]

[1]Department of Internal Medicine, Division of Endocrinology, State University of New York, Downstate Medical Center, Brooklyn, New York, USA

[2]Department of Medicine, Division of Endocrinology, New York University, NY, USA

Abstract

Background: Ovarian hyperstimulation syndrome (OHSS) is a rare but serious complication of ovarian stimulation occurring during assisted reproduction technologies (ART). It is characterized by increased vascular permeability and hypercoagulable states resulting in strokes and peripheral ischemia. Acute myocardial infarction and cardiac thrombosis, however, have been rarely reported complications of OHSS.

Methods: A literature search was performed for reports on myocardial infarction and cardiac thrombosis associated with ovarian stimulation with a summary of their clinical characteristics.

Results: A total of twelve published cases were reviewed with 5 out of 12 (41.67%) of the reported cases were 35 years of age or older. Myocardial infarction was reported in 10 out of the 12 cases (83.3%). Two of the cases were pregnant at presentation (16.67%). The mean duration between starting ovarian stimulation medications and clinical presentation was 23 days. Chest pain was the most common presenting symptom (66.67%), 2 cases presented with stroke (16.67%) and 2 cases presented with abdominal distention (16.67%). A total of 8 patients underwent coronary angiography with 2 of these cases were treated with percutaneous coronary intervention. No mortality reported in any of the twelve cases.

Conclusion: Women of a relatively younger age undergoing ovarian stimulation may be at risk for developing myocardial infarction and cardiac thrombosis. Once thrombosis is suspected, initiating appropriate therapy in a timely manner is crucial.

Keywords

Ovarian Stimulation; Cardiac Thrombosis; Myocardial Infarction; Ovarian Hyperstimulation Syndrome

[*]**Corresponding author:** Samy I McFarlane, MD, MPH, MBA, FACP, Distinguished Teaching Professor and Associate Dean College of Medicine, Department of Medicine, Division of Endocrinology Internal Medicine Residency Program Director, State University of New York, Downstate Medical Center, 450 Clarklson Ave, Box 50, Brooklyn, NY 11203-2098, USA, Tel: 718-270-6707; Fax: 718-270-4488; smcfarlane@downstate.edu.

Introduction

The use of ovarian stimulation has increased exponentially over the past few decades, as there have been significant advancements in reproductive technology. However, with increased use of ovarian stimulation, there have been reports of increasing numbers of ovarian hyperstimulation syndrome (OHSS) and hypercoagulable states despite protocols in place to minimize these complications [1]. Ovarian hyperstimulation syndrome is a complication which affects women taking hormonal medications to stimulate oocyte development in the ovaries, which can cause serious psychological and physiological derangements and, in rare cases, may leads to maternal death [2]. Ovarian hyperstimulation syndrome is classified according to disease severity as mild, moderate or severe. It is characterized by ovarian enlargement, fluid shifts into the third space, hypovolemia, hemoconcentration, serosal effusions, ascites and renal failure; and in some cases, hypercoagulation [3]. Multiple case reports of ovarian stimulation-associated cardiac thrombosis have been published. The aim of this systematic review of the case reports is to describe the clinical characteristics of cardiac thrombosis in these cases. We also aim to provide a brief literature review on the subject.

Methods

On October 2018, a systematic search was conducted using PubMed and Google Scholar to review case reports about myocardial infarction or cardiac thrombosis precipitated by ovarian stimulation. Studies that listed the keywords “Myocardial infarction, cardiac thrombosis, ovarian stimulation, ovarian hyperstimulation syndrome” were used to identify case reports. The reference list of each report was checked for additional cases. Data reviewed included demographic data, cardiovascular risk factors, medication(s) used for ovarian stimulation, parity, thrombophilia, electrocardiography (EKG), cardiac enzymes, echocardiography, time of presentation, complications, management, and outcome.

Results

A total of 12 cases were identified and summarized in table 1 [4–15]. The patients were in the age group of 22 to 41 years and the mean age was 32.7 ± 17.5 years, median age was 34.5 years. From the cases 5 out of 12 (41.67%) were 35 years of age or older.

Two of the cases were pregnant at presentation (16.67%). Prevalence of cardiovascular risk factors and co-morbidities in the reported cases were as follows: hypertension, diabetes and obesity in 1 case (8.33%), active smoking in 3 cases (25%), antiphospholipid syndrome in 2 cases (16.67%), polycystic ovarian disease in 3 cases (25%), 1 case with bicuspid aortic valve (8.33%), and 1 case of premature ovarian failure (8.33%). Most of the reported cases presented with chest pain (66.67%), 2 cases presented with stroke (16.67%) and 2 cases presented with abdominal distention (16.67%). The mean time between starting ovarian stimulation medications and presentation was 23 days. Elevated troponin levels were reported in 8 cases (66.67%). Management of myocardial infarction associated with ovarian stimulation included anticoagulation (low molecular weight heparin and heparin), antiplatelet therapy (aspirin and clopidogrel). Supportive therapy was provided to all acses in

the form of correction of hypoalbuminemia and intravenous fluid replacement. A total of 8 patients underwent coronary angiography, with two of them treated with percutaneous coronary intervention. Therapeutic abortion was not utilized in the two reported pregnant patients. One case was treated with surgical intervention due to an associated sinus of valsalva aneurysm. One case was complicated with a cerebrovascular accident. No mortalities were reported in any of the cases.

MI: myocardial infarction, EKG: Electrocardiogram, Cath: cardiac catheterization, rFSH: recombinant follicle stimulating hormone, HCG: human chorionic gonadotropin, GRHa: gonadotropin-releasing hormone agonist, LH: luteinizing hormone, HMG: human menopausal gonadotropin, LAD: left anterior descending artery, RPDA: right posterior descending artery, PCI: percutaneous coronary intervention, AC: anticoagulation, AP: antiplatelet, STEMI: ST-segment elevation myocardial infarction.

Discussion

Coronary heart disease is still, despite medical advancements, the leading cause of death in adults. The American Heart Association (AHA) has reported that 15.5 million person's ≥20 years of age in the USA have coronary heart disease [16]. It causes about one-third of all deaths in the population older than 35 years [17]. Myocardial infarction in young females are commonly due to coronary artery thrombosis from hypercoagulable states such as antiphospholipid syndrome, protein S and factor XII deficiencies; embolization, spasm, dissection, accelerated thrombosis, or coronary anomalies [18,19].

In this review, we reported 9 cases of myocardial infarctions and 3 cases of cardiac thrombosis, related to ovarian stimulation. The pathophysiology of ovarian hyperstimulation syndrome is not completely understood. It is likely that when the ovaries are exposed to exogenous stimulating hormones there is a cascade of proinflammatory mediator production such as vascular endothelial growth factor (VEGF), interleukins, tumor necrosis factor-α, and endothelin-1; which mediates increases in vascular permeability and capillary leakage into the third space [20]. These changes will lead to hemoconcentration, hypovolemia, hypercoagulable states and renal dysfunction. On the other hand, ascites and ovarian enlargement contribute to decreased venous return which in turn precipitates thrombus formation [21]. Co-morbidity of hypercoagulable states such as antiphospholipid syndrome can increase the risk of thrombosis as in the two cases in our review [7,10]. The majority of the cases in the review, however, had no history of hypercoagulable states, which indicate that OHSS can be considered as a risk factor for hypercoagulability leading to thrombosis and myocardial infarction.

Management of myocardial thrombosis associated with OHSS is hydration, anticoagulation and antiplatelet therapy. Percutaneous coronary intervention should be considered in all cases of myocardial infarction given the reports of favorable outcomes. Literature support the success of PCI with or without coronary artery stenting in hypercoagulable states as in antiphospholipid syndrome [22]. In the cases of OHSS with MI during pregnancy, PCI is still recommended as Coronary angiography exposes patients to 2.5–5.0 mSv (equivalent to 125–250 chest x-rays), and PCI exposes patients to 5.0–15.0 mSv (equivalent to 115–1000

chest x-rays); both are below the threshold for teratogenicity at any gestational age [23]. The use of thrombolytic therapy in pregnancy is still debatable as there is no scientific data on its safety [24].

Conclusion

Myocardial infarction and cardiac thrombosis are very serious complications of OHSS. Women undergoing ovarian stimulation may be at risk for developing thrombosis secondary to OHSS. Detailed assessment before ovarian stimulation is essential to detect history of preexisting hypercoaguable conditions or previous history of thrombosis that may necessitate the consideration of alternative infertility interventions in these high-risk patients. Furthermore, once OHSS is diagnosed prompt therapy should be instituted including supportive therapy such as fluid replacement and close monitoring to minimize the risk of these potentially fatal complications.

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References

1. Chan WS (2009) The ‘ART’ of thrombosis: a review of arterial and venous thrombosis in assisted reproductive technology. Curr Opin Obstet Gynecol 21: 207–218. Link: https://goo.gl/yYWurt [PubMed: 19276806]
2. Whelan JG 3rd, Vlahos NF (2000) The ovarian hyperstimulation syndrome. Fertil Steril 73: 883–896. Link: https://goo.gl/74ReCn [PubMed: 10785212]
3. Golan A, Ron-el R, Herman A (1989) Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Surv 44: 430–440. Link: https://goo.gl/kmYLjQ [PubMed: 2660037]
4. Ludwig M, Tölg R, Richardt G (1999) Myocardial Infarction Associated With Ovarian Hyperstimulation Syndrome. JAMA 282: 632–633. Link: https://goo.gl/RS5Fch [PubMed: 10517713]
5. Worrell GA, Wijdicks EFM, Eggers SDZ, Phan T, Damario MA, et al. (2001) Ovarian hyperstimulation syndrome with ischemic stroke due to an intracardiac thrombus. Neurology 57: 1342–1344. Link: https://goo.gl/rJr9K4
6. Akdemir R, Uyan C, Emiroglu Y (2002) Acute myocardial infarction secondary thrombosis associated with ovarial hyperstimulation syndrome. Int J Cardiol 83: 187–189. Link: https://goo.gl/z4eT2w [PubMed: 12007695]
7. Andrejevic S, Bonaci-Nikolic B, Bukilica M, Macut D, Miljic P, et al. (2002) Intracardiac thrombosis and fever possibly triggered by ovulation induction in a patient with antiphospholipid antibodies. Scand J Rheumatol 31: 249–251. Link: https://goo.gl/g1RG2c [PubMed: 12369659]
8. Girolami A, Scandellari R, Tezza F, Paternoster D, Girolami B (2007) Arterial thrombosis in young women after ovarian stimulation: case report and review of the literature. Send to J Thromb Thrombolysis 24: 169–174. Link: https://goo.gl/25TuKQ
9. Coli S, Magnoni M, Melisurgo G, Persico P, Doldi N, et al. (2007) Myocardial infarction complicating the initial phase of an ovarian stimulation protocol. Int J Cardiol 115: e56–57. Link: https://goo.gl/GQvL3K [PubMed: 17067704]
10. Giner V, Oltra MR, Esteban MJ, García-Fuster MJ, Salvador A, et al. (2007) Catastrophic antiphospholipid syndrome related to severe ovarian hyperstimulation. Clin Rheumatol 26: 991–993. Link: https://goo.gl/Mj5ao5 [PubMed: 16538387]

11. Duran JR, Raja ML (2007) Myocardial infarction in pregnancy associated with clomiphene citrate for ovulation induction: a case report. J Reprod Med 52: 1059–1062. Link: https://goo.gl/8uVeqW [PubMed: 18161408]
12. Ravel P, Marcaggi X, Ferrier N, Vignancour S, Clerfond G, et al. (2009) Myocardial infarction and ovarian stimulation: case report. Ann Cardiol Angeiol 58: 313–317. Link: https://goo.gl/bdBhh7
13. Zamirian M, Moaref AR, Alavi SH, Zarrabi K (2012) Right ventricular thrombus: a rare complication of ovarian hyperstimulation syndrome. Int Cardiovasc Res J 6: 131–132. Link: https://goo.gl/rfBF8S [PubMed: 24757608]
14. Abuzeyad FH, Ibnaouf ES, Farras MA (2017) Clomiphene Associated Inferior STEMI in a Young Female due to Right Coronary Artery Dissection. Case Rep Emerg Med 2017: 4747831 Link: https://goo.gl/hRfNCu [PubMed: 28593057]
15. Avşar S, Öz A, Avşar A, Kaya A, Börklü EB (2018) Acute myocardial infarction associated with clomiphene citrate in a young woman. Turk Kardiyol Dern Ars 46: 401–405. Link: https://goo.gl/646wEp [PubMed: 30024398]
16. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. (2016) American Heart Association Statistics Committee, Stroke Statistics Subcommittee. Executive Summary: Heart Disease and Stroke Statistics−-2016 Update: A Report From the American Heart Association. Circulation 133: 447–454. Link: https://goo.gl/8Tk71L [PubMed: 26811276]
17. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, et al. (2008) American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics−-2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 117: e25–146. Link: https://goo.gl/3fscFM [PubMed: 18086926]
18. Williams MJA, Restieaux NJ, Low CJS (1998) Myocardial infarction in young people with normal coronary arteries. Heart 79: 191–194. Link: https://goo.gl/HUQDEh [PubMed: 9538315]
19. Mc Gill HC, McMahan CA, Zieske AW (2000) Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. Circulation 102: 375–379. Link: https://goo.gl/z7XeGw
20. Evbuomwan IO, Davison JM, Murdoch AP (2000) Coexistent hemoconcentration and hypoosmolality during superovulation and in severe ovarian hyperstimulation syndrome: a volume homeostasis paradox. Fertil Steril 74: 67–72. Link: https://goo.gl/gxaCGx [PubMed: 10899499]
21. Lamazou F, Legouez A, Letouzey V, Grynberg M, Deffieux X, et al. (2011) Ovarian hyperstimulation syndrome: Pathophysiology, risk factors, prevention, diagnosis and treatment]. J Gynecol Obstet Biol Reprod 40: 593–611. Link: https://goo.gl/LWYMLw
22. Takeuchi S, Obayashi T, Toyama J (1998) Primary antiphospholipid syndrome with acute myocardial infarction recanalised by PTCA. Heart 79: 96–98. Link: https://goo.gl/MhU7n8 [PubMed: 9505929]
23. Conti CR (2009) cardiovascular studies and the radiation dose. Clin Cardiol 32: 56–57. Link: https://goo.gl/GQF14q [PubMed: 19215017]
24. Gartman (2013) The use of thrombolytic therapy in pregnancy. Obstet Med 6: 105–111. Link: https://goo.gl/x8Swkg [PubMed: 27708701]

Table 1:

Summary of acute myocardial thrombosis associated with ovarian stimulation

Name/ Year	Age	Parity	Medication	Timing of Symptom	EKG	Echocardiography	Cath	Treatment	Outcome
Ludwig, 1999 [4]	35	0	rFSH; HCG	3	Anterior MI	Akinesia of anterior wall	Distal LAD occlusion	PCI	Alive
Worrell, 2001 [5]	34	0	GRHa; rFSH	7	Normal	Left ventricular thrombus		AC	Alive
Akdemir, 2002 [6]	26	0	GRHa; rFSH; HCG	30	Anterior MI		Normal	Streptokinase	Alive
Andrejevic, 2002 [7]	28	3	Clomiphene; HMG; HCG		Normal	Left atrial thrombus		AC	Quadruplet; one survived
Girolami, 2007 [8]	40	0	HCG; LH	20	Anterolateral MI			AP, AC	Alive
Coli, 2007 [9]	38	0	GRHa; rFSH	12	Normal	Inferior akinesis	Normal	AP, AC	Alive
Giner, 2007 [10]	35	5	rFSH: HMG	40	Anteroseptal MI	Hypokinesia of anteroseptal wall	Saccular aneurysm with LMCA compression	Surgery	Alive
Duran, 2007 [11]	33	0	Clomiphene	35	Anterolateral MI		Normal	AC, AP	Normal delivery
Ravel, 2007 [12]	25	0	GRHa; rFSH	7	Lateral ischemia	Inferolateral hypokinesia	Normal	AP, AC	Alive
Zamiria, 2012 [13]	22	0	Clomiphene; HCG	90	Normal	Right intraventricular thrombus		AC	Alive
Abuzeyad, 2017 [14]	41	0	Clomiphene	5	Inferior STEMI		RPDA dissection	AP, AC	Alive
Avşar, 2017 [15]	36	0	Clomiphene	5	Anterior STEMI	Apical akinesis; anterolateral hypokinesis	LAD occlusion	PCI	Alive