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Case Report

Obstetrics and Gynaecology Section

Massive Haemoperitoneum Postovulation: A Rare Complication of Unmonitored Anticoagulant Therapy

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ABSTRACT

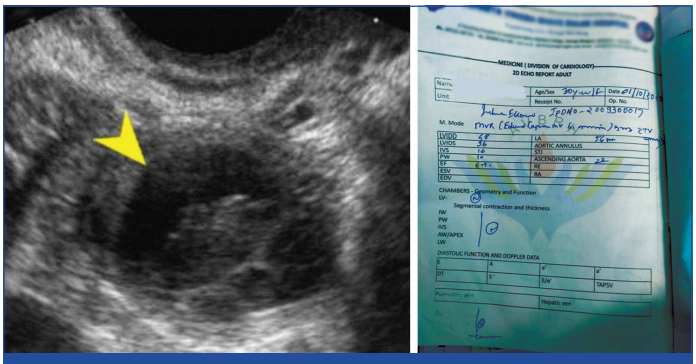
Derangements in coagulation profile due to ongoing anticoagulant medication can complicate the most primitive physiology in a woman, ovulation. Unmonitored anticoagulant therapy can lead to an array of complications, one of which is intraperitoneal haemorrhage secondary to numerous medical and surgical conditions. The resultant haemoperitoneum can cause sudden hypovolemic shock, especially in a patient with compromised cardiovascular status. This report narrates the case of a 30-years-old nulliparous female patient on anticoagulant therapy, operated for multiple cardiac defects and developed massive haemoperitoneum as a consequence of ovulation. The patient presented in shock to the Emergency Department with unstable haemodynamic status. A multi-disciplinary approach to the case converged on ruptured functional ovarian cyst as a working diagnosis. Conservative management of haemoperitoneum was decided upon, whereby correcting shock and providing pro-coagulant therapy along with blood products was the main line of management. All efforts failed soon after when the cyst wall ruptured catastrophically, leading to collapse of the general condition of the patient. Surgical approach was undertaken and a ruptured ovarian cyst wall was identified to be the cause. The cyst wall was subsequently repaired electrosurgically and the patient recovered well with an uneventful postoperative period. However, the characteristic feature of this case is the lack of follow-up due to lockdown restrictions of this continuum, the Coronavirus Disease-2019 (COVID-19) pandemic. The management of such cases must be carefully titrated, keeping in mind the risks and benefits of both pro-coagulant and anti-coagulant therapy wherein one can jeopardise the effects of the other.

Keywords: Corpus luteal cyst, Intraperitoneal haemorrhage, Warfarin

CASE REPORT

This is the case of a 30-year-old unmarried nulliparous female patient presented to the Gynaecological Emergency unit with complaints of palpitations, breathlessness and pain in abdomen for three days with menorrhagia for the last two cycles. The patient complained of dull abdominal ache for two months that gradually progressed to persistent, severe abdominal pain in the last three days, worsened with movement and change in decubitus. The patient was a known case of rheumatic heart disease with severe mitral stenosis, severe tricuspid stenosis with superimposed tricuspid regurgitation and pulmonary hypertension. The patient had undergone mitral valve replacement with tricuspid annuloplasty 12 years ago and started on anticoagulant medication- oral warfarin (4 mg/day on alternate days), lasix-spironolactone (20-50 mg twice daily), diltiazem (90 mg daily), digoxin (0.25 mg daily). She gave history of stroke and right sided hemiplegia with seventh cranial nerve palsy a year ago and recovered well from the episode. Her last menstrual period was 16 days before presentation with regular 30-day cycles. She did not complain of fever or bleeding from any natural orifices and history of congenital and familial bleeding disorders was unremarkable.

On examination, her Body Mass Index (BMI) was 22.4 kg/m^2, Blood Pressure (BP) was 90/60 mmHg, pulse rate 126 beats/min, Partial Oxygen Saturation (SpO_2) 98% on room air, raised jugular venous pressure of 8 cm H_2O with normal respiratory examination. Her abdomen examination revealed abdominal distension with marked tenderness in left iliac fossa and hypogastrium and per vaginal examination showed tenderness in all fornices. Her haemoglobin was 5.3 gm%, White Blood Cells (WBC) 9900 cells/dL, platelets 1,86,000 cells/dL and haematocrit 15.2%. Prothrombin Time (PT) was 55.8 s with an International Normalised Ratio (INR) 4.46 and a Partial Thromboplastin Time (PTT) 57 s. Pregnancy was subsequently ruled out by urine pregnancy test and β-Human Chorionic Gonadotropin (HCG) level <2.39 mIU/mL. Liver and renal function tests were within normal limits and Cancer Antigen (CA)-125 levels showed 364 U/mL. Both direct and indirect Coomb's tests were negative. Haemoglobin (Hb) electrophoresis for sickle cell disease was also negative. Ultrasound of the abdomen was suggestive of a complex ovarian cyst on left side measuring approx. 84×72 mm with mild ascites haemoperitoneum [Table/Fig-1]. A two-dimensional (2D)-echocardiography revealed dilated atria, severe tricuspid regurgitation, severe pulmonary artery hypertension with 60% ejection fraction [Table/Fig-2].



[Table/Fig-1]: Ultrasound image of (yellow arrow) complex ovarian cyst.
[Table/Fig-2]: A 2D-Echocardiography report. (Images from left to right)

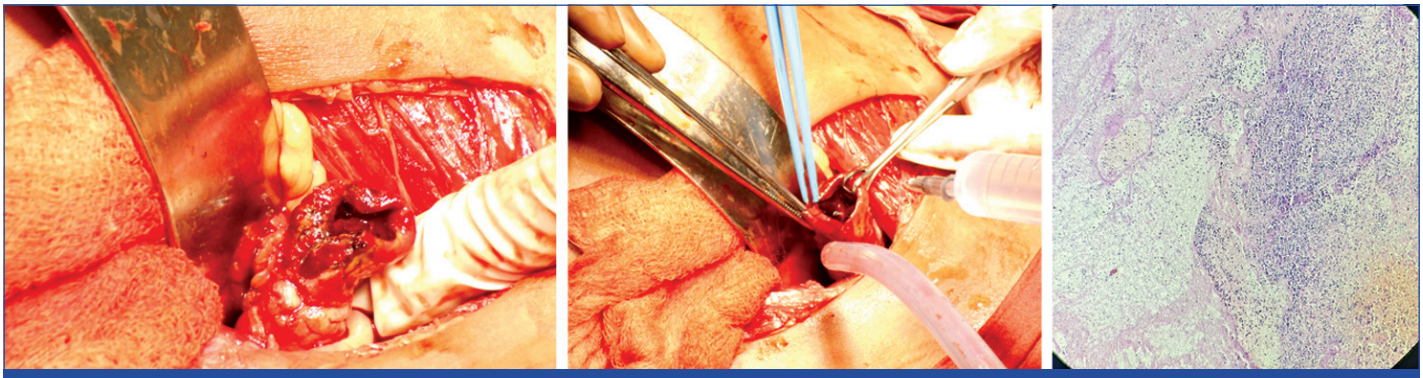
Ectopic pregnancy was ruled out with a negative urine pregnancy test. Above findings were suggestive of a functional ovarian cyst rupture with mild haemoperitoneum secondary to anticoagulant therapy. Investigations undertaken by the patient seven months ago showed a normal coagulation profile.

A multidisciplinary team of physicians, cardiac surgeons and gynaecologists decided upon a conservative line of management since the general condition of the patient did not necessitate the

need for surgical exploration. Anticoagulants were tapered down in consultation with the cardiothoracic surgery team. Tranexamic acid formed the mainstay of management. Tranexamic acid (3 g/day IV in divided doses) was started and three units of Packed Red Cell (PRC) units and 7 units of Fresh Frozen Plasma (FFP) were transfused and the patient gradually showed improvement. However, on day three of admission, she had an episode of syncope with feeble pulse, tachycardia with 160 beats/min and hypotension 80/40 mmHg. An emergency exploratory laparotomy was undertaken.

Exploratory laparotomy revealed approx. 1300 mL of haemoperitoneum including approximately 250 g of clots. Left sided ruptured ovarian cyst was identified with active bleeding from cyst wall and ovarian tissues appeared normal on both sides [Table/Fig-3]. The cyst wall was excised electrosurgically [Table/Fig-4]. Visceral organs were examined intraoperatively and there was no evidence of bleeding, endometriosis or adhesions. Urogenital and peritoneal surfaces appeared unremarkable. Two units PRC and four units Fresh Frozen Plasma (FFP) were transfused intraoperatively. The aim of the surgery was to identify and control the source of bleeding and to drain the haemoperitoneum. Conservation of fertility was paramount to the patient and formed the core of management despite surgical methods being implemented to control the bleeding. Ruptured corpus luteal cyst was a retrospective diagnosis but the aetiology was ovulation with defective coagulation.

Histopathological examination of the incisional biopsy revealed an otherwise unremarkable corpus luteal cyst wall [Table/Fig-5]. The section from the cyst wall tissue was stained with Haematoxylin and Eosin (H&E) and examination under 100x magnification showed the luteal cyst wall containing a well-organised thrombus with areas of red blood cells, surrounding fibrin accumulations, and scattered leucocytes.



[Table/Fig-3]: Ruptured corpus luteal cyst, intraoperative photograph. **[Table/Fig-4]:** Cyst wall excised electrosurgically. **[Table/Fig-5]:** Histopathological examination of ruptured cyst wall, H&E stain with 100x magnification. (Images from left to right)

She was discharged on Oral Contraceptives (OC) (0.03 mg ethinyl oestradiol with 0.15 mg levonorgestrel) for three months to suppress ovulation. Coagulation profile was advised after 15 days, followed by monthly till therapeutically acceptable INR of 1.5 after which three monthly monitoring was to be undertaken. The couple was counselled on family planning and pre-conceptional dose modification.

DISCUSSION

As the case unfolded, it became clear that the patient was unmonitored on oral anticoagulants due to the ongoing pandemic and rupture of a corpus luteal cyst produced catastrophic haemoperitoneum in the patient. Normally, women may present with 'mittelschmerz', characterised by abdominal-pelvic pain during ovulation due to rupture of a mature follicle with subsequent bleeding into the peritoneal cavity [1].

At the time of ovulation, in a patient with defective haemostasis, blood fills in the ruptured follicle to form corpus haemorrhagicum. This collection eventually bleeds into the peritoneal cavity forming haemoperitoneum causing persistent peritoneal irritation or sometimes directly into the broad ligament forming a retroperitoneal haematoma [2]. But it was ruled out due to the complex loculated appearance on ultrasound and appearance of symptoms [3]. A clinically differentiating factor is that haemoperitoneum primarily due to a ruptured corpus luteum occurs closer to ovulation as compared to postovulatory presentation of a corpus haemorrhagicum [4]. It was critical to rule out ectopic pregnancy by β-HCG levels as ruptured ectopic pregnancy has a similar presentation [5].

Non Steroidal Anti-inflammatory Drugs are the preferred analgesics but they must be used cautiously due to their anti-platelet activity. Alternatives like opioids then form the analgesics of choice in these patients [6]. A compilation of cases of ruptured functional ovarian cysts is as given in [Table/Fig-6] [1-3,5,7-9].

In haemodynamically stable patients, haemostatic therapy can be initiated, comprising primarily of oral tranexamic acid (upto 4 g/day in divided doses). Oral tranexamic acid is usually well tolerated and can often be administered in a synergistic combination with oral hormonal therapy [10]. Newer treatment modalities including Plasma Cell Concentrates (PCC) and Recombinant Activated Factor VIIa (rFVIIa) are available but lack of substantial evidence and high cost were deterrents in the present case [9]. In women on anticoagulants, a ruptured corpus luteal cyst with haemoperitoneum is fatal in 3-11% and can recur in nearly 25-31% of the cases. There is a substantial risk of haemorrhage in patients with an INR of 3.0-4.5 and increases exponentially for values >4.5 [11].

Oral Contraceptives (OCs) are the mainstay of treatment for patients with defective haemostasis. OCs suppresses ovulation and subsequent formation of corpus luteum to prevent similar events in future [12]. OC regulate endometrial growth and control shedding, thereby reducing dysmenorrhoea and other menstrual complaints. Long-term OCs obviate the use of blood products and their associated complications during conservative management of such episodes. Blood products also carry a risk of transmission of Human Immunodeficiency Virus (HIV) and hepatitis viruses, though these complications are extremely rare with the advancements in screening and processing of blood products. Conception must be preceded by suspension of OCs with serial follicular ultrasound studies with thorough, multidisciplinary evaluation of anticoagulant therapy during antepartum and peripartum period. Complications at the time of delivery can be managed by blood products and supportive therapy [3,11].

Newer generation intrauterine contraceptive systems containing levonorgestrel (LNG-IUS) retain efficacy upto seven years and are effective alternatives to OCs [13]. They function by curtailing endometrial proliferation and subsequently decrease menstrual blood loss and pain. LNG-IUS is relatively inert to menstrual irregularities and also provides easy reversibility of fertility [14]. Gonadotropin-releasing hormone (GnRH) analogues such as leuprolide acetate and goserelin injected subcutaneously offer similar efficacy in suppressing ovulation and menstrual complaints. However, their use is limited by their hypoestrogenic side effects such as hot flashes and reduced bone density, coupled with high

S. No.	Author's name and year	Place of study	Presentation	Aetiology	Diagnosis	Management
1	Cetinkaya SE et al., 2011 [1]	Ankara, Turkey	Acute abdomen with massive haemoperitoneum (defibrinated blood) and bilateral ovarian cysts	Congenital afibrinogenemia	Periovulatory bleeding with haemoperitoneum	1st episode: Exploratory laparotomy with cystectomy and evacuation of haemoperitoneum 2nd episode: Conservative management
2	Agarwal M et al., 2017 [5]	Shillong, India	Acute abdomen with distension and breathing difficulty	Warfarin therapy postmitral valve replacement	Ruptured corpus luteum with haemoperitoneum	Conservative
3	Payne JH et al., 2007 [2]	Sheffield, UK	Case 1: Acute abdomen with haemoperitoneum	Factor VII deficiency	Ruptured corpus luteal cyst with haemoperitoneum	Conservative
			Case 2, 1st presentation: Acute abdomen with chest pain 2nd presentation: Acute abdomen	Factor X deficiency with congenital diaphragmatic hernia	Left ovarian endometriotic cyst with haemoperitoneum and secondary haemothorax	Laparotomy and left oophorectomy
					Enlarged right ovary with moderate ascites	Conservative
			Case 3, 1st presentation: Acute abdomen 2nd presentation: Acute abdomen with ascites	Sitosterolemia (ABCG5 gene mutation)	Right ovarian cyst	Laparotomy with right oophorectomy
					Multiple left ovarian haemorrhagic cysts with ? haematosalpinx	Conservative
4.	Özdemir S 2019 [7]	Istanbul, Turkey	Marked thickening of terminal ileum and sigmoid colon	Warfarin for prophylaxis of deep vein thrombosis secondary to lung mass	Colonic intramural haematoma	Conservative management
5.	Sikka P et al., 2015 [8]	Chandigarh, India	Complex left ovarian cyst haemorrhage with acute abdomen and gross peritoneal free fluid	Long term warfarin post mitral valve replacement	Corpus luteal haemoperitoneum	Conservative management
6.	Ara A et al., 2016 (Case series) [9]	New Delhi, India	2 cases presenting in acute abdomen with haemoperitoneum secondary to complex ovarian cyst haemorrhage	Long term warfarin post mitral valve replacement	Ruptured Complex ovarian cysts	Both cases: Conservative management
7.	Bottini E et al., 1991 [3]	Milano, Italy	Case 1: Acute abdomen with intraperitoneal bleeding	Von Willebrand Factor (vWF) and Factor VIII deficiency.	Ruptured Corpus luteum postovulation leading to haemoperitoneum	Laparotomy with wedge resection of ovary
			Case 2: Haemoperitoneum secondary to complex ovarian cyst	Von Willebrand Factor (vWF) and Factor VIII deficiency	Ruptured complex ovarian cyst leading to haemoperitoneum.	Conservative due to allergic reaction to cryoprecipitate
			Case 3: Acute abdomen with haemoperitoneum	Congenital afibrinogenemia	Haemorrhagic corpus luteum	Laparotomy and wedge resection of ovary
8.	Present study	Wardha, India	Acute abdomen with haemoperitoneum	Long term warfarin therapy post mitral valve replacement	Ruptured corpus luteal cyst with haemoperitoneum secondary to coagulation defect	Exploratory laparotomy with electrosurgical excision of cyst wall

[Table/Fig-6]: Cases of unmonitored anticoagulant therapy [1-3, 5, 7-9].

cost for long-term therapy. Surgical line of management must be undertaken only with the aid of advanced laboratory support and an experienced haematologist. In cases like these, every effort to preserve fertility must be taken using a combination of conservative surgery, high-dose hormonal therapy with haemostatic drugs [10].

Careful history, examination and plan of action must be well documented and explaining follow-up of investigations and medications is paramount to long-term management of the patient. A system of follow-up of high-risk cases must be developed to prevent such recurrences.

CONCLUSION(S)

Anticoagulant and anti-platelet medications need stringent follow-up and the patients must be informed in detail, the duration and dosage of medication. Contraceptive therapy must be individualised for every couple after considering desire to conceive in the future. Surgical line of management must be undertaken cautiously weighing the benefits and all short- and long-term complications for the patient.

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