



CASE REPORT

**UPDATED** Delayed intra-abdominal bleeding following trans-vaginal ultrasonography guided oocyte retrieval for *in vitro* fertilization in patients at risk for thrombo-embolic events under anticoagulant therapy [v2; ref status: indexed, <http://f1000r.es/24f>]

Roy Mashiach<sup>1,2</sup>, David Stockheim<sup>1,2</sup>, Mati Zolti<sup>1,2</sup>, Raoul Orvieto<sup>1,3</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Ramat Gan, Israel  
<sup>2</sup>Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel  
<sup>3</sup>Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel

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**Abstract**

We report herein, two cases of massive delayed (2 and 4 days) intra abdominal hemorrhage following ovum pick-up (OPU), in patients at risk for thrombo-embolic events, who concomitantly used therapeutic doses of low molecular weight heparin (LMWH). We discuss the possible mechanisms involved in causing the aforementioned delayed bleeding, and call for re-evaluation of the presently accepted anticoagulant co-treatment regimen. These case reports should direct physicians' attention and keep them alert, while conducting IVF treatment to this subgroup of high risk patients.

**Article Status Summary**

**Referee Responses**

Referees	1	2	3
<b>v1</b> published 16 Sep 2013	 report	 report	 report
		1	1
<b>v2</b> published 18 Oct 2013 <b>UPDATED</b>	 report		

1 **Fatma Ferda Verit**, Suleymaniye Maternity, Research and Training Hospital Turkey

2 **Pedro Barri**, Institut Universitari Dexeus of the Universitat Autònoma de Barcelona Spain

3 **William Ledger**, University of New South Wales Australia

**Latest Comments**

No Comments Yet

**Corresponding author:** Raoul Orvieto ([raoul.orvieto@sheba.health.gov.il](mailto:raoul.orvieto@sheba.health.gov.il))

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**UPDATED Changes from Version 1**

In response to the feedback from our reviewers, we have now added more details on the methods used for follicle aspiration. The follicles were aspirated by experienced physicians using a fine (19 G) needle (William A. Cook Australia PTY LTD, Australia) and 140 mmHg suction pressure, puncturing each ovary once, without reinserting the needle through the vaginal wall.

We believe that the presently accepted anticoagulant co-treatment regimen, including the dose and timing of administration, should be challenged and undergo a critical re-evaluation, i.e. delaying [24 h after the procedure] and reducing the first dose [half] of LMWH post OPU, with gradual increments [after 2 days of half a daily dose]. However, whether this modification will increase the tendency toward thrombosis should be further investigated [by multidisciplinary experts]. Additional comments on the reviewers' queries can be found in the author response box underneath the reviewers' reports.

**See referee reports**

**Introduction**

Nowadays, ultrasonographically guided trans-vaginal ovum pick-up (OPU) is considered an accepted and safe method for oocyte retrieval worldwide. Nevertheless, the multiple punctures of the vaginal vault can injure or tear the vaginal mucosa, ovaries, intra-abdominal organs or blood vessels, resulting in mild to severe internal and external bleeding and other complications<sup>1,2</sup>. Clinically significant blood loss after OPU is actually uncommon<sup>3</sup>, with a reported incidence of severe intra- or retroperitoneal bleeding varying from 0 to 1.3%<sup>2</sup>.

Intraperitoneal bleeding tends to be severe with acute hemodynamic deterioration, whereas retroperitoneal bleeding usually has a later and more indolent presentation. Intra-abdominal bleeding should be suspected immediately after OPU with the development of signs and symptoms of anemia. While a drop in hemoglobin concentration is an indication for prompt blood transfusion, hemodynamic deterioration dictates surgical intervention with subsequent hemostasis. Most of cases are diagnosed several hours following OPU, with a reported interval between OPU and surgical intervention, ranging from 3 to 18 hours<sup>4,5</sup>.

In patients with an underlying coagulopathy, the interval between OPU and the appearance of clinical signs and symptoms of severe intra-abdominal bleeding or surgical intervention, was reported to be longer. While, Battaglia *et al.*<sup>6</sup> reported a 3 hour interval between OPU and surgical intervention in a patient with coagulation factor XI deficiency<sup>6</sup>, intervals of 2 and 10 days, were reported in patients suffering from essential thrombocythemia<sup>7</sup> and factor VIII deficiency<sup>8</sup>, respectively. Notably, none of the aforementioned patients were treated with anticoagulant medications.

The situation is even more complicated for women with known thrombophilia and/or history of a thrombo-embolic event, who use anticoagulant drugs. The hitherto published research regarding this issue is scarce, with only one study reporting on 24 patients treated concomitantly with anticoagulation therapy, who underwent 68 oocyte retrieval procedures<sup>9</sup>. Since IVF treatment was not associated with

any medical complication, such as bleeding or thromboembolic complications, Yinon *et al.* have concluded that among patients considered as high risk for a thromboembolic event, the introduction of low molecular weight heparin (LMWH), as a cycle protective treatment, is safe<sup>9</sup>.

Here, we report two cases of massive delayed intra-abdominal-hemorrhage following OPU, in patients at risk for thromboembolic events, who concomitantly used LMWH. These cases aim to direct physicians' attention and keep them alert, while treating this subgroup of at risk patients.

**Case report**

Two patients were referred to our IVF clinic for egg/embryos collection for surrogacy because of the risk associated with pregnancy. Both were under therapeutic doses of LMWH, which according to a senior haematologist consultant, were co-administered during the controlled ovarian hyperstimulation (COH) for IVF, until 16 h before the oocyte retrieval and resumed 12 h after the procedure. In both cases, the follicles were aspirated by experienced physicians using a fine (19 G) needle (William A. Cook Australia PTY LTD, Australia) and 140 mmHg suction pressure. In each ovary, the follicles were sequentially punctured without reinserting the needle through the vaginal wall. This study was approved by the institutional review board of Sheba Medical Centre.

**Case 1:**

A 37-year-old patient with essential thrombocytosis, was diagnosed incidentally following routine examination 7 years ago. One year ago, she developed sinus vein thrombosis, necessitating therapeutic doses of anticoagulant therapy. Controlled ovarian hyperstimulation included the multidose GnRH antagonist protocol, with follicle stimulating hormone (FSH) daily dose of 112.5 to 150 IU. She achieved a peak E2 level of 1538 pmol/l with one leading follicle at each ovary. OPU was reported as uneventful with a retrieval of 3 oocytes, of which 2 were fertilized and cryopreserved. A routine complete blood count (CBC) 2 h following OPU revealed a stable hemoglobin (Hb) concentration, as compared to her baseline level (9.92 g/dL vs 10.52 g/dL, respectively).

Two days following OPU she was re-admitted to our ward, because of severe abdominal and shoulder pain, abdominal bloating and tenesmus. On physical examination her abdomen was swollen and tender, with floating blood as evidenced by transabdominal ultrasonography. She was hospitalized and closely observed hemodynamically. During the next 4 h, her Hb concentration dropped to 7.2 g/dL with clinical deterioration, mandating resuscitation, and urgent exploration.

During exploratory laparoscopy, a massive hemoperitoneum was found (approximately 2.5 L of blood), and a profuse bleeding was observed from a large vein in the posterior aspect of the left infundibulo-pelvic ligament. The vessel was successfully coagulated. The patient was transfused with 4 units of blood, 3 unit of cryoprecipitate, and 2 units of fresh frozen plasma. Her postoperative course was uneventful and she was discharged 4 days later with a hemoglobin level of 9.4 g/dL.

## Case 2:

A 32-year-old patient, suffering from Budd–Chiari syndrome as a consequence of a myeloproliferative disorder, necessitating therapeutic doses of anticoagulant therapy. Controlled ovarian hyperstimulation included the long GnRH agonist protocol, with HMG daily dose of 375 to 450 IU. She achieved a peak E2 level of 2349 pmol/l with four leading follicles at both ovaries. OPU was reported as technically uneventful, however no oocytes were retrieved (empty follicles).

Three days following OPU, the patient started to feel unwell and complained of lower abdominal pain and dyspnea with stable Hb concentration (10.43–10.95 g/dL). A day later, she gradually became pale, tachycardiac, with a drop in Hb level (8.84 g/dL) that continued (8.66 g/dL) despite a blood transfusion, mandating urgent exploratory laparoscopy. During laparoscopy, a massive hemoperitoneum was observed (approximately 2.5 L of blood), with an active bleeding from a tear of the right ovarian capsule. The tear was successfully coagulated with an accurate hemostasis. The patient was transfused with 5 units of blood, and 2 units of fresh frozen plasma. Her post-operative course was uneventful and she was discharged a week later with a hemoglobin level of 11.68 g/dL.

## Discussion

We report herein, to our knowledge, the first 2 cases of massive delayed intra-abdominal hemorrhage following OPU, in patients at risk for thromboembolic event, who concomitantly used *therapeutic* doses of LMWH. We are not aware of any guidelines that have been published by any professional society, regarding OPU under LMWH. Moreover, since most guidelines relate to patients undergoing surgeries that may apply strict hemostatic measures, which are not available during US guided OPU, our report challenges and calls for re-evaluation of the anticoagulation regimen, provided to this subgroup of at risk patients, during an IVF treatment cycle.

Following OPU, the cessation of bleeding requires the interaction of the injured blood vessel with the circulating platelets and clotting proteins in order to form a stable platelet-fibrin clot. Any abnormalities of these factors may result in clinically significant bleeding. In the present cases, both patients received therapeutic doses of LMWH (enoxaparin, 60mg bid), which were discontinued 16 h prior to OPU and resumed 12 h after the procedure. Moreover, intra abdominal bleeding occurred 2 and 4 days following OPU.

Several plausible mechanisms might be responsible for the aforementioned delayed bleeding: (a) early postoperative use of enoxaparin and unfractionated heparin was reported to be associated with a significant increase in re-exploration for postoperative bleeding, often at a significantly delayed time period after the initial surgery<sup>10</sup>. Moreover, this delay was especially common with enoxaparin; (b) while the effect of LMWH and unfractionated heparin on the coagulation cascade is well established, we may wonder whether these substances also affect the fibrin nanostructure, which plays a major role in the mechanical strength and lysis of clots. Yeronahos *et al.*<sup>11</sup> provided quantitative evidence showing that both

LMWH and unfractionated heparin, independent of their other actions on the coagulation cascade, directly alter the nanostructure of fibrin fibers, contributing to improved fibrinolysis.

We therefore believe that the presently accepted anticoagulant co-treatment regimen, including the dose and timing of administration, should be challenged and undergo a critical re-evaluation. For example, delaying (*24 h after the procedure*) and reducing the first dose (*half*) of LMWH post OPU, with gradual increments (*after 2 days of half a daily dose*) might offer some advantages. However, whether this modification will increase the tendency toward thrombosis, should be further investigated by a *multidisciplinary experts*. Moreover, since intra abdominal bleeding obviously occurs, and may occur several days following OPU, we recommend that the patient be kept in the ward for observation for at least 2–4 days following OPU.

In the presented cases we also observed a tear of the ovarian capsule and an inadvertent puncture of a blood vessel within the infundibulopelvic ligament. Both complications might have been prevented by meticulous follicular aspiration using a small diameter aspiration needle (19G), and preferably under the guide of color Doppler ultrasonography<sup>12</sup>, respectively.

In conclusion, massive delayed intra-abdominal hemorrhage may occur following OPU, in patients at risk for thromboembolic event, who concomitantly used LMWH. These case-reports should direct physicians' attention and keep them alert, while conducting an IVF treatment to this subgroup of high risk patients.

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## Author contributions

Roy Mashiah: coordinated and participated in the patients' treatment, contributed to the discussion, assisted in writing the paper and edited it in all its revisions.

David Stockheim: participated in the patients' treatment, contributed to the discussion, assisted in writing the paper and edited it in all its revisions.

Mati Zolti: participated in the patients' treatment, contributed to the discussion, assisted in writing the paper and edited it in all its revisions.

Raoul Orvieto: the principal investigator, designed the study, participated in the patients' treatment, contributed to the discussion, assisted in writing the paper and edited it in all its revisions.

## Competing interests

No competing interests were disclosed.

## Grant information

The author(s) declared that no grants were involved in supporting this work.

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[PubMed Abstract](#) | [Publisher Full Text](#)

## Current Referee Status:

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### Referee Responses for Version 2



**Pedro Barri**

Department of Obstetrics, Gynaecology and Reproduction, Institut Universitari Dexeus of the Universitat Autònoma de Barcelona, Barcelona, Spain

**Approved: 27 November 2013**

**Referee Report:** 27 November 2013

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.



**Fatma Ferda Verit**

Department of Obstetrics and Gynecology, Suleymaniye Maternity, Research and Training Hospital, Istanbul, Turkey

**Approved: 21 October 2013**

**Referee Report:** 21 October 2013

I accept this article as it stands.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

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### Referee Responses for Version 1



**William Ledger**

Obstetrics and Gynaecology, University of New South Wales, Sydney, Australia

**Approved: 30 October 2013**

**Referee Report:** 30 October 2013

This article is built around 2 case reports of clinically significant intra-abdominal bleeding in the days following egg collection for the purposes of IVF, in patients receiving therapeutic doses of Heparin. The authors use the case reports as a focus for discussion of the management of patients prescribed this

medication prior to IVF.

The reports are provisionally novel to warrant publication. The use of English is somewhat idiosyncratic and requires minor review. The text preceding the first case report includes the suggestion that both eggs and embryos may be collected for surrogacy. Only eggs can be collected, and this should be amended.

The most important part of the article is in the discussion. The authors suggest a review of anticoagulant co-treatment in the light of their cases. I do not think that their experience would be sufficient risk of thrombotic complications. This problem is mentioned but should be further highlighted by the authors. I would also suggest they further emphasize the use of a smaller gage aspiration needle for egg collection in these higher risk cases.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

## 1 Comment

### Author Response

**Raoul Orvieto**, Director, Infertility and IVF Unit, Sheba Medical Center, Israel

Posted: 03 Nov 2013

We would like to thank Prof. Ledger for his valuable comments.

Eggs were collected and fertilized, and the embryos were frozen for future FET cycles to the surrogate. The issue of the thrombotic risk and the suggestion of a smaller gage needle both appear in the 2nd version.

**Competing Interests:** No competing interests were disclosed.



**Pedro Barri**

Department of Obstetrics, Gynaecology and Reproduction, Institut Universitari Dexeus of the Universitat Autònoma de Barcelona, Barcelona, Spain

**Approved: 09 October 2013**

**Referee Report:** 09 October 2013

This is an observational case-report on two cases of delayed intra-abdominal bleeding following OPU for IVF in patients under anticoagulant therapy.

This article is acceptable, but some changes should be included:

1. There is no information either on the type of needles used for aspiration, or on the aspiration pressure.
2. Why does a young patient (32 yrs) have a negative OPU?
3. How many needle punctures have been performed?
4. There is no information on the outcomes of the oocytes retrieved in case 1.
5. The discussion section is well structured, but authors should present a final recommendation on daily doses and the duration of LMWH.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

## 1 Comment

### Author Response

**Raoul Orvieto**, Director, Infertility and IVF Unit, Sheba Medical Center, Israel

Posted: 10 Oct 2013

We would like to thank Prof. Barri for his valuable comments.

1. The follicles were aspirated by experienced physicians using a fine (19 G) needle (William A. Cook Australia PTY LTD, Australia) and 140 mmHg suction pressure.
2. The negative OPU was unexplained (empty follicle?).
3. Punctures were started in the ovary with the follicles closest to the vagina, and each follicle was sequentially punctured without reinserting the needle through the vaginal wall.
4. In case 1, OPU was reported as uneventful with a retrieval of 3 oocytes, of which 2 were fertilized and cryopreserved.
5. As we already mentioned and further clarify: "We therefore believe that the presently accepted anticoagulant co-treatment regimen, including the dose and timing of administration, should be challenged and undergo a critical re-evaluation. For example, delaying [24 h after the procedure] and reducing the first dose [half] of LMWH post OPU, with gradual increments [after 2 days of half a daily dose] might offer some advantages. However, whether this modification will increase the tendency toward thrombosis, should be further investigated [by multidisciplinary experts]. Moreover, since intra abdominal bleeding obviously occurs, and may occur several days following OPU, we recommend that the patient be kept in the ward for observation for at least 2–4 days following OPU."

**Competing Interests:** No competing interests



**Fatma Ferda Verit**

Department of Obstetrics and Gynecology, Suleymaniye Maternity, Research and Training Hospital, Istanbul, Turkey

**Approved: 02 October 2013**

**Referee Report:** 02 October 2013

I think this article can be accepted without any revisions. The paper quality is good and it adds new knowledge to the literature.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

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