Association between peak estradiol levels and ovarian torsion among symptomatic patients receiving gonadotropin treatment

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Received: 5 December 2016 / Accepted: 3 March 2017 / Published online: 15 March 2017
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Abstract

Purpose Ovarian torsion is a surgical emergency that can be clinically challenging to diagnose. Patients who have received assisted reproductive technologies (ART) are a subset of women with an increased risk for torsion. As the ART population continues to increase, there is a need to delineate risk factors for the development of ovarian torsion in this unique population. A pilot study was performed to determine the proportion of patients with suspected ovarian torsion who have received ART and to identify possible diagnostic biomarkers for ovarian torsion among these patients.

Methods A single institution retrospective cohort study of patients taken to surgery for suspected ovarian torsion over a 5-year period.

Results During the study period, 171 patients were taken to surgery for suspected ovarian torsion. Patients receiving ART constituted 19 (11%) of these patients. Among the 19 fertility treatment patients, 16 had received treatment with gonadotropins, 10 of which had surgically confirmed ovarian torsion. These ten patients had higher preoperative peak estradiol levels (3122 versus 1875 pg/mL, $p = 0.05$) and a larger

ovarian diameter (9.7 versus 7.6 cm, $p = 0.05$) than the six patients receiving gonadotropins found to not have ovarian torsion.

Conclusions These results suggest infertility treatment using gonadotropins for ovarian hyperstimulation may be an independent risk factor for ovarian torsion as suggested by the disproportionate number of such individuals represented in the study population (9% of all patients, 84% of fertility patients). Additionally, among women taking gonadotropins, an association exists between peak estradiol levels, ovarian diameter, and risk for ovarian torsion.

Keywords Ovarian torsion · Adnexa · Peak estradiol · Infertility · Gonadotropins

Introduction

Ovarian torsion is a rarely encountered process in the general population, accounting for only 2.7% of gynecologic surgical emergencies [1]. One subset of female patients who have previously been identified as at risk for development of torsion are those undergoing controlled ovarian hyperstimulation with gonadotropins for assisted reproduction. Though the incidence of ovarian torsion is low among patients receiving gonadotropin therapy for egg retrieval (0.13%), the risk of ovarian torsion increases to 0.6% in patients who conceive spontaneously using gonadotropins for ovulation induction and further increases to 7.5% in the setting of ovarian hyperstimulation syndrome (OHSS) diagnosed using the World Health Organization classification system [2–4].

For the ART patient population, the increased risk of torsion is thought to be due to iatrogenic enlargement of the ovaries, which can occur during ovarian hyperstimulation, as it has been established that an ovarian cyst >5 cm is an

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independent predictor of torsion in all female patients presenting to the emergency department with symptoms concerning for torsion [5–7]. Unfortunately, ovarian torsion remains a surgical diagnosis as the most common symptoms (nausea, vomiting, and abdominal pain) are non-specific, and no sonographic findings have proven definitive [8–11]. For this reason, women are taken to the operating room for suspected ovarian torsion on clinical suspicion alone; ultimately 53–56% of patients who undergo surgical management are found not to have ovarian torsion [1, 12, 13]. This highlights the importance of developing a diagnostic algorithm for improving the preoperative diagnosis of ovarian torsion. The importance of such an algorithm is further emphasized by the emergent nature of torsion requiring expedient surgical intervention and correction to avoid loss of gonadal function [14, 15].

As the number of women utilizing controlled ovarian hyperstimulation increases, there is a need to delineate risk factors for the development of ovarian torsion in this unique population [16, 17]. The objective of this study is to define the incidence of recent fertility treatment among women being operated on for presumed ovarian torsion, establish risk factors for ovarian torsion in this population, and provide recommendations to guide decision making for women having recently received fertility treatments presenting with acute abdominal pain.

Methods

Study design

This is a retrospective cohort study of cases selected from a tertiary academic medical center in Boston, MA. Following IRB approval, the operative notes from all gynecologic surgeries performed from 2006 to 2010 at the hospital were reviewed, and those indicating the patient was taken to the operating room for suspicion of ovarian torsion were identified. The medical records for these cases were then reviewed. The decision to proceed with surgical management for presumed ovarian torsion was made by the attending physician taking into account the patient's overall physical exam, laboratory values, and findings on ultrasound with Doppler evaluating ovarian size, location, blood flow, and presence of free fluid in the abdomen.

Variables

Variables of interest including age, gravidity, parity, presenting symptoms, history of fertility treatment, laboratory findings, radiologic findings, and intraoperative diagnosis were abstracted from the patients' electronic medical records, and all patient identifiers were removed.

Patients were categorized as having undergone recent fertility treatment if treatment was received within 30 days of surgery, or if the patient was pregnant as a result of such treatment at the time of surgery. The fertility treatments that were identified included gonadotropin therapy for egg retrieval or ovulation induction, clomiphene citrate therapy, and transfer of IVF donor egg. To assess the effect of ovarian stimulation on torsion, we undertook an analysis of the fertility treatment group who underwent controlled ovarian hyperstimulation and ovulation induction with gonadotropins.

Statistics

Descriptive statistics included medians and intraquartile ranges (IQR). The proportion of patients with surgically confirmed torsion between women receiving fertility treatment and those not receiving fertility treatment was compared using Fisher's exact test. Among women who received fertility treatment, we correlated the incidence of ovarian torsion with peak estradiol levels and ovarian size using the Wilcoxon rank-sum test. All statistical analysis was completed using SAS 9.2 [18].

Results

During the study period, 171 patients presenting to the emergency department were taken to surgery for suspicion of ovarian torsion. Of these patients, 19 (11%) had received fertility treatment within 30 days of surgery or were pregnant as a result of such treatments. Characteristics of patients undergoing surgery for suspicion of torsion are shown in Table 1. No statistically significant differences were found between the two groups for symptom duration or whether torsion was confirmed at surgery. Overall, patients taken to surgery for suspicion of torsion were found to have torsion only 58% of the time. We found no difference in incidence of surgically confirmed torsion by fertility treatment history (63% utilized treatment, 58% did not; p value 0.8). The chosen surgical approach was either laparoscopy or abdominal laparotomy in 77.2 and 22.8% of cases, respectively. In the group with confirmed ovarian torsion, 57% received detorsion of the involved ovary and 43% received an oophorectomy. In the group of patients confirmed not to have ovarian torsion, 16% required an oophorectomy for other indications. In the fertility treatment group, all of the patients with confirmed ovarian torsion received detorsion.

Among patients with recent fertility treatment, fourteen had undergone controlled ovarian hyperstimulation with gonadotropins for IVF (74%), two had gonadotropin ovulation induction (11%), two received clomiphene citrate (11%), and one was pregnant after donor egg IVF (5%) (Table 2). Among

Table 1 Characteristics of patients taken to for surgery for suspicion of ovarian torsion by fertility treatment status

	Fertility treatment (<i>n</i> = 19)	No fertility treatment (<i>n</i> = 152)	<i>p</i> value
Gravidity, median (IQR)	1 (1–3)	1 (0–2)	0.13
Parity, median (IQR)	0 (0–1)	0 (0–1.5)	0.5
Age, median years (IQR)	32 (31–38)	30 (24–37)	0.04
Pregnant, <i>n</i> (%)	9 (47)	21 (14)	<0.01
Symptom duration, median days (IQR)	2 (1–3)	1 (1–3)	0.8

IQR intraquartile range

ART patients surgically diagnosed with ovarian torsion, ultrasound reports were often equivocal (50%). Among the seven fertility treatment patients not found to have torsion at the time of surgery, four had no abnormality on surgical exploration (57%), two had features of ovarian hyperstimulation syndrome (29%), and one had a heterotopic gestation (14%). Of the ART patients with intrauterine pregnancy at the time of surgery, the average gestational age at presentation was 10.1 weeks (2.4–20.3 weeks). Six had live births (66%), two had ongoing pregnancies at last contact (22%), and one was lost to follow up (11%). Of the ART patients who were not pregnant at the time of surgery, the average time from initiation of ART treatment to presentation in the emergency department was 14.4 days (8–20 days).

Among the 16 patients taken to surgery for suspicion of torsion who had received gonadotropins for ovarian stimulation (for IVF or IUI), those surgically diagnosed with ovarian torsion had higher median peak serum estradiol levels (3122 versus 1875 pg/mL, $p = 0.05$) and larger ovaries by ultrasound measurement (largest median dimension 9.7 versus 7.6 cm, $p = 0.05$) than patients who were not found to have ovarian torsion (Table 3). There were no differences in BMI between the two groups.

Table 2 Descriptive statistics for ART patients who were operated on for suspected ovarian torsion

	Ovarian torsion confirmed surgically (<i>n</i> = 12)	Ovarian torsion ruled out surgically (<i>n</i> = 7)	Proportion of ART patients (<i>n</i> = 19)
Gonadotropins for controlled ovarian hyperstimulation, <i>n</i> (%)	9 (75)	5 (71)	14 (74)
Gonadotropins for ovulation induction, <i>n</i> (%)	1 (8)	1 (14)	2 (11)
Clomiphene citrate	2 (17)	0 (0)	2 (11)
Donor egg IVF	0 (0)	1 (14)	1 (5)

Discussion

While it is known that the risk of ovarian torsion is increased in women undergoing controlled ovarian hyperstimulation, data are lacking regarding the prevalence of fertility treatment patients among all women presenting with suspected ovarian torsion [2–4, 19]. In the present series, fertility treatment patients represented 11% of women undergoing surgical evaluation for suspected ovarian torsion. As the number of patients undergoing infertility treatment continues to increase, it is becoming increasingly important to recognize how this unique population compares to non-ART patients when presenting with signs and symptoms consistent with ovarian torsion.

The clinical diagnosis of ovarian torsion remains challenging. Our analysis revealed that for all-comers being operated on for suspected ovarian torsion, only 58% had a correct pre-operative diagnosis, despite the use of ultrasound with Doppler to assist in making a diagnosis. Comparatively, in 1985, Hibbard published that 47% of patients taken to the operating room with presumed ovarian torsion were correctly diagnosed pre-operatively [1]. The persistent inability to definitively diagnose torsion pre-operatively further supports the need for continued efforts to establish tools to improve diagnostic accuracy for this condition.

Efforts have been made to identify laboratory and radiologic values which could improve the diagnostic accuracy for ovarian torsion, but this has proven difficult due to the snapshot of information that one can obtain in the Emergency Department. We recognize that patients receiving fertility treatments are a unique subset in that they have lab values that are closely trended during their treatment to monitor response to therapy. One specific value, estradiol, is followed in women who receive ovulation induction with gonadotropins in order to survey ovarian reserve, determine ovarian response prior to egg retrieval, and to screen for OHSS [20–23]. Among women who had undergone ovarian stimulation with gonadotropins, we found a significant association with peak estradiol levels and surgical diagnosis of ovarian torsion. This has potential clinical applications when evaluating abdominal pain

Table 3 Diagnostic variables for ovarian torsion among patients receiving gonadotropin therapy

	Torsion confirmed (<i>n</i> = 10)	No evidence of torsion (<i>n</i> = 6)	<i>p</i> value
Peak E2 (pg/mL), median (IQR)	3122 (2230–3525)	1875 (1492–2372)	0.05
Ovarian size (cm in greatest dimension), median (IQR)	9.7 (7.9–10.3)	7.6 (7.2–8.0)	0.05

IQR intraquartile range

in this patient population. Additionally, we compared ovarian size as this is a known risk factor for torsion in the general female population. In this 16 patient case series, we found that fertility patients also follow this trend as the largest median dimension of the ovaries with torsion was more than 2 cm greater in diameter when compared to ovaries without torsion (9.7 versus 7.6 cm).

A novel aspect of this study is the association of torsion with elevated estradiol levels associated with the use of gonadotropins. Of note, typical features of OHSS include hemoconcentration, oliguria, electrolyte imbalances, and abdominal bloating secondary to ascites. For patient undergoing controlled ovarian hyperstimulation, varying degrees of these aforementioned symptoms may occur. Accordingly, one might not anticipate torsion as frequent given the perivascular exudate that suspends the ovaries. The elevated estradiol may be a secondary reflection of the state of ovarian enlargement; larger series will be needed to evaluate if these risk factors are independent.

Being descriptive in nature, this retrospective study has some other limitations. Selection bias may occur when determining which women are offered surgery for a diagnosis of presumed ovarian torsion. We are unable to ensure that all surgeons used consistent and similar criteria for diagnosing ovarian torsion pre-operatively meaning some women with ovarian torsion may have not undergone an operation. Moreover, clinicians might be more or less conservative in surgical management in women undergoing ART due to the financial and physical investments of fertility treatment. Another limitation is the sample size, which is a result of studying a relatively rare diagnosis at a single institution. On the other hand, by limiting data collection to one institution, all lab results and ultrasound reports were determined using similar equipment and technique, decreasing practice variation. Additionally, this ensures that the women in the fertility treatment group were exposed to similar fertility work-up, treatment, and monitoring protocols.

In conclusion, our findings suggest that among women who have undergone ovarian stimulation with gonadotropins and present with possible ovarian torsion, peak estradiol levels and ovarian volume are associated with surgical confirmation of ovarian torsion. Given our small sample size, this warrants further investigation in a larger cohort of women. This would

also allow us to better define diagnostic criteria for the immediate surgical intervention for management of suspected ovarian torsion in these patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights For this type of study formal consent is not required.

References

- Hibbard LT. Adnexal torsion. *Am J Obstet Gynecol*. 1985;152:456–61.
- Govaerts I, Devreker F, Delbaere A, Revelard P, Englert Y. Short-term medical complications of 1500 oocyte retrievals for in vitro fertilization and embryo transfer. *Eur J Obstet Gynecol Reprod Biol*. 1998;77:239–43.
- Kemmann E, Ghazi DM, Corsan GH. Adnexal torsion in menotropin-induced pregnancies. *Obstet Gynecol*. 1990;76:403–6.
- Mashiach S, Bider D, Moran O, Goldenberg M, Ben-Rafael Z. Adnexal torsion of hyperstimulated ovaries in pregnancies after gonadotropin therapy. *Fertil Steril*. 1990;53:76–80.
- Huchon C, Staraci S, Fauconnier A. Adnexal torsion: a predictive score for pre-operative diagnosis. *Hum Reprod*. 2010;25:2276–80. doi:10.1093/humrep/deq173.
- Linam LE, Darolia R, Naffaa LN, Breech LL, O'hara SM, Hillard PJ, Huppert JS. US findings of adnexal torsion in children and adolescents: size really does matter. *Pediatr Radiol*. 2007;37:1013–9. doi:10.1007/s00247-007-0599-6.
- Pena JE, Ufberg D, Cooney N, Denis AL. Usefulness of Doppler sonography in the diagnosis of ovarian torsion. *Fertil Steril*. 2000;73:1047–50.
- Bouguizane S, Bibi H, Farhat Y, Dhifallah S, Darraji F, Hidar S, Lassoued L, Chaieb A, Khairi H. Adnexal torsion: a report of 135 cases. *J Gynecol Obstet Biol Reprod (Paris)*. 2003;32:535–40.
- Chang HC, Bhatt S, Dogra VS. Pearls and pitfalls in diagnosis of ovarian torsion. *Radiographics*. 2008;28:1355–68. doi:10.1148/rg.285075130.
- Huchon C, Fauconnier A. Adnexal torsion: a literature review. *Eur J Obstet Gynecol Reprod Biol*. 2010;150:8–12. doi:10.1016/j.ejogrb.2010.02.006.
- Mashiach R, Melamed N, Gilad N, Ben-Shitrit G, Meizner I. Sonographic diagnosis of ovarian torsion: accuracy and predictive factors. *J Ultrasound Med*. 2011;30:1205–10.
- Bar-On S, Mashiach R, Stockheim D, Soriano D, Goldenberg M, Schiff E, Seidman DS. Emergency laparoscopy for suspected

- ovarian torsion: are we too hasty to operate? *Fertil Steril*. 2010;93: 2012–5. doi:[10.1016/j.fertnstert.2008.12.022](https://doi.org/10.1016/j.fertnstert.2008.12.022).
13. Cohen SB, Weisz B, Seidman DS, Mashlach S, Lidor AL, Goldenberg M. Accuracy of the preoperative diagnosis in 100 emergency laparoscopies performed due to acute abdomen in non-pregnant women. *J Am Assoc Gynecol Laparosc*. 2001;8:92–4.
 14. Bayer AI, Wiskind AK. Adnexal torsion: can the adnexa be saved? *Am J Obstet Gynecol*. 1994;171:1506–10. discussion 1510–1
 15. Ozcan C, Celik A, Ozok G, Erdener A, Balik E. Adnexal torsion in children may have a catastrophic sequel: asynchronous bilateral torsion. *J Pediatr Surg*. 2002;37:1617–20.
 16. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2014 Assisted Reproductive Technology National Summary Report. Atlanta (GA): US Dept of Health and Human Services; 2016
 17. Wang J, Sauer MV. In vitro fertilization (IVF): a review of 3 decades of clinical innovation and technological advancement. *Ther Clin Risk Manag*. 2006;2:355–64.
 18. SAS Institute Inc. SAS/STAT® 9.2 User's Guide. Cary, NC: SAS Institute Inc.; 2008.
 19. Hasson J, Tsafir Z, Azem F, Bar-On S, Almog B, Mashlach R, Seidman D, Lessing JB, Grisaru D. Comparison of adnexal torsion between pregnant and nonpregnant women. *Am J Obstet Gynecol*. 2010;202:536.e1–6. doi:[10.1016/j.ajog.2009.11.028](https://doi.org/10.1016/j.ajog.2009.11.028).
 20. Arslan M, Bocca S, Mirkin S, Barroso G, Stadtmayer L, Oehninger S. Controlled ovarian hyperstimulation protocols for in vitro fertilization: two decades of experience after the birth of Elizabeth Carr. *Fertil Steril*. 2005;84:555–69.
 21. Elchalal U, Schenker JG. The pathophysiology of ovarian hyperstimulation syndrome—views and ideas. *Hum Reprod*. 1997;12: 1129–37.
 22. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE working group on poor ovarian response definition ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the bologna criteria. *Hum Reprod*. 2011;26:1616–24. doi:[10.1093/humrep/der092](https://doi.org/10.1093/humrep/der092).
 23. Licciardi FL, Liu HC, Rosenwaks Z. Day 3 estradiol serum concentrations as prognosticators of ovarian stimulation response and pregnancy outcome in patients undergoing in vitro fertilization. *Fertil Steril*. 1995;64:991–4.