The effects of oral calcium on the prevention of moderate to severe ovarian hyperstimulation syndrome in high-risk patients: A placebo-controlled study

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Abstract: Ovarian Hyperstimulation Syndrome (OHSS) is a serious complication of Assisted Reproductive Technology (ART). Some studies show that intravenous calcium infusion decreases the risk of OHSS in high-risk patients. Some life-threatening complications may occur following intravenous calcium gluconate infusion, but oral calcium carbonate is a cheap and easy-to-use medication with no/minor side-effects. The present clinical trial was therefore designed to identify the role of oral calcium in OHSS prevention in high-risk patients. A total of 99 patients who had received an antagonist protocol for ovarian stimulation in their ART cycles and were at risk of OHSS were recruited for the study. The patients were allocated into two groups to receive either 500-mg BID calcium carbonate tablets or placebo tablets from their puncture date for five days. The findings showed no significant differences in oocyte and grade A, B and C embryo counts between the two groups. Moreover, the clinical pregnancy rate and the frequency of OHSS symptoms were not significantly different between the two groups. The frequencies of mild, moderate and severe OHSS were not significantly different between the two groups either. Since oral calcium is an easy-to-use method with limited side-effects, we recommend further studies to examine its effects on OHSS prevention in high-risk patients.

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In this research they work on drugs are effective in prevention of ovarian hyperstimulation syndrome (OHSS). Ovarian hyperstimulation syndrome (OHSS) is a serious complication of assisted reproductive technology (ART) and identify of best drug for prevention of this complication is a target for this research group. Email: zhrrezaee@yahoo.com

PUBLIC INTEREST STATEMENT

We conduct the present study because ovarian hyperstimulation syndrome (OHSS) is a serious complication of assisted reproductive technology (ART). Some studies show that intravenous calcium infusion decreases the risk of hyperstimulation syndrome in high-risk patients. Some life-threatening complications may occur following intravenous calcium gluconate infusion. But oral calcium carbonate is a cheap and easy-to-use drug with no/minor side effects. So we designed this study to identify the role of oral calcium in hyperstimulation syndrome prevention in high-risk patients.
1. Introduction

Ovarian Hyperstimulation Syndrome (OHSS) is a serious but uncommon complication of Assisted Reproductive Technology (ART). Moderate to severe OHSS occurs in 1–5% of ART cycles. OHSS causes major signs and symptoms, including increased vascular permeability following fluid accumulation in the third space that leads to ascites and abdominal overdistention (American Society for Reproductive medicine, Birmingham, Alabama, 2016). The signs of OHSS are classified according to their intensity and time of initiation. Severe OHSS can cause serious complications, such as pleural effusion, renal failure and thromboembolism (American Society for Reproductive medicine, Birmingham, Alabama, 2016).

The classic pathophysiology of OHSS is arterial dilatation and increased capillary permeability, which cause body fluids to shift from intravascular to extravascular spaces. This fluid shift results in a hypovolemic hyponatremia state (Bergh & Navot, 1992; Geva and Jaffe, 2000; Practice Committee of the American Society for Reproductive Medicine, 2016). Severe OHSS is a hypovolemic status caused by the shift of fluids to the third space and the consequent increase in serum hematocrit (Manno & Tome, 2008). All hypovolemic conditions lead to secondary reactive hyperaldosteronism by renin-angiotensin cascade activation (Manno & Tome, 2008). A direct relationship has previously been reported between plasma renin activity and the severity of OHSS (Bergh & Navot, 1992; Practice Committee of the American Society for Reproductive Medicine, 2016). In women with OHSS, the concentration of angiotensin II is higher in the follicular and ascitic fluid than in the plasma (Fernandez et al., 1985; Nastri, Ferriani, Rocha, & Martins, 2010). Renin is an enzyme produced and activated in the juxtaglomerular (JG) cells of the afferent arterioles in the kidney (Keeton & Campbell, 1980). Renin secretion is positively regulated by the “second messenger” cyclic adenosine monophosphate (cAMP). Moreover, the secretion of renin from the JG cells is inversely related to the extracellular and intracellular calcium concentrations (Navot et al., 1987).

An increase in plasma calcium concentration generally inhibits renin release through a signal found in other renin-stimulated conditions, such as low dietary salt intake (Anand, Jenifer, & Williams, 2015; Atchison, Ortiz-Capisano, & Beierwaltes, 2010; Isaac, Raymond, Rainfray, & Ardaillou, 1984). Decreased extracellular and intracellular calcium, on the other hand, stimulates renin secretion in vitro. Some studies have shown that in vivo calcium-renin interactions are similar to in vitro interactions. The acute activation of calcium-sensing receptor inhibits renin release (Antonipillai & Horton, 1985; Beierwaltes, 2010; Fray, Park, & Valentine, 1987) and decreases vascular endothelial growth factor (VEGF) (El-Khayat & Elsadek, 2015). VEGF is believed to have a critical role in the pathophysiology of OHSS (Pellicer et al., 1999).

Some methods proposed for OHSS prevention include the identification of high-risk patients (those with a prior history of OHSS), the use of different methods of ovarian stimulation, e.g. low-dose follicle-stimulating hormone (FSH) and gonadotropin-releasing hormone (GnRh) antagonists, and the use of prophylactic methods for intra-ovarian stimulation (e.g. cycle cancellation, freezing of all embryos, and GnRh antagonist administration) (El-Khayat & Elsadek, 2015; Gurgan et al., 2011; Naredi & Karunakaran, 2013).

Waleed EI-Khayat investigated the effects of intravenous calcium in OHSS prevention and found that intravenous calcium decreases the risk of OHSS without affecting the pregnancy rate (El-Khayat & Elsadek, 2015). Timur Gurgan evaluated the effects of the intravenous infusion of calcium
Some complications may occur following intravenous calcium gluconate infusion, particularly with rapid infusion. They include arrhythmias with concomitant cardiac glycoside use, end organ damage due to intravascular ceftriaxone-calcium precipitates, tissue necrosis and calcinosis, hypotension, bradycardia, arrhythmias and aluminum toxicity. Some of these side-effects are life-threatening [www.Drugs.com, Home/Professionals/FDAPI/Calcium gluconate Injection (2018)]. Since patients with OHSS are prone to electrolyte imbalances (Fábregues et al., 1999), some physicians prefer not to use intravenous calcium for OHSS prevention.

Oral calcium carbonate is a cheap and easy-to-use medication with no/minor side-effects. The possible (but definitely not life-threatening) side-effects of the drug include constipation, upset stomach or vomiting, stomach ache and the loss of appetite [www.Drugs.com, Home/Drugs A to Z/Calcium carbonate/Side Effects (2018)]. This study hypothesized that oral calcium can be effective in the prevention of moderate to severe OHSS and was designed to identify the role of oral calcium in OHSS prevention in high-risk patients.

2. Material and methods

This clinical trial recruited 99 patients who received an antagonist protocol for ovarian stimulation in ART cycles and were therefore at risk of OHSS. The study was conducted from September 2017 to August 2018 at Yas Hospital, Tehran, Iran. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences. The IRCT code for the project is IRCT201704170349ON2. The patients were allocated to two groups to receive either 500-mg BID calcium carbonate tablets (Kharazmi Pharmaceutical Company, Iran) or identical placebo tablets from their puncture date for five days.

The subjects were included if they had received an antagonist protocol at the beginning of their ART cycles, had more than 20 oocytes with a mean follicle diameter over 20 mm and had serum estradiol levels over 2500 pg/ml. The subjects were excluded if they had endocrine disorders (e.g. diabetes mellitus, Cushing’s disease and congenital adrenal hyperplasia), systemic diseases (e.g. asthma), collagen vascular diseases, hypercholesterolemia, sickle cell anemia, a history of neoplasm and serum estradiol levels over 5000 pg/ml (which increased the risk of severe OHSS). The subjects who used insulin sensitizing medications or had a cancelled cycle were also excluded.

All the patients received an antagonist protocol for ART, their medical history was recorded, underwent physical examination and had their body mass index (BMI) calculated. The anti-Müllerian hormone (AMH) levels of all the patients were checked and compared between the two groups. Transvaginal sonography was performed for all the patients on the second or third day of menstruation. Gonadotropins, including recombinant FSH (Gonal-f®, Merck) and human menopausal gonadotropin (hMG) (Merional or Menogon, Ferring, IBSA) and urinary FSH (Fostimone, IBSA) were started according to age, antral follicle count (AFC) and AMH. The dose of gonadotropin was 75–300 units. Serial transvaginal sonograms were obtained from each patient and the dose of gonadotropins was adjusted according to follicle size and ovarian response. In the antagonist protocol, the antagonist was administered using two methods; in the fixed method, the antagonist (Cetrotide® 0.25 mg/day, Merck Serono) was administrated on the sixth day after the initiation of gonadotropin; in the flexible method, the antagonist (Cetrotide® 0.25 mg/day, Merck Serono) was administered when the largest follicle size achieved became 13 mm. The serum estradiol levels of all the patients were checked on the day of hCG, recombinant hCG or GnRh agonist injection.

When the follicle size reached 18–20 mm, 10,000 IU of hCG (Darou Pakhsh or PDHMOG or Organon), 250 µg of recombinant hCG (Ovitrelle, Merck Serono) or 0.1 mg of GnRh agonist injection
(Ipsen, Ferring) were administered. Oocytes were obtained 36 hours after hCG or recombinant hCG injection and 35 hours after GnRh agonist injection.

All the patients were hospitalized for at least one day after their ovarian puncture. The patients were carefully monitored, regularly visited and evaluated in terms of OHSS signs and symptoms. The complete blood count (CBC) test was performed for all the patients one day after ovarian puncture. Seven days after their discharge from the hospital, the patients were revisited and reevaluated through transvaginal sonography. After investigating all the signs and symptoms of OHSS, the patients at a higher risk of OHSS were hospitalized. All the patients were trained about the symptoms of OHSS and asked to visit the hospital if they developed any symptoms. The patients were passively observed for one month. Participants’ OHSS symptoms were classified as mild, moderate or severe based on Navot’s classification (Navot, Bergh, & Laufer, 1992). Finally, the calcium and placebo groups were compared in terms of the prevalence of mild, moderate and severe OHSS.

3. Statistical analysis
Data were collected in special forms and entered into Stata. Missing and outlier data were then evaluated. The descriptive (secondary) goals of the study were evaluated using mean, standard deviation (SD) and other dispersion indexes for the quantitative variables. For the qualitative variables, the ratio of the number of patients scoring positive in that characteristic to all the patients in each group was measured and presented as a percentage.

The corresponding graphs were then drawn. In order to test the analytical hypothesis, the Chi-square test was used for the qualitative and the independent t-test for the quantitative variables. Since the normal distribution of data is an assumption for performing the t-test, the Kolmogorov Smirnov test was applied to evaluate the normality of the data.

4. Results
A total of 99 patients were recruited for this study. Eight patients from the calcium group were excluded as they did not take their calcium tablets properly and missed some of the doses. Moreover, three patients from the placebo group and two from the calcium group were lost to follow-up and were thus also excluded. A total of 86 patients remained until the end of the study. The mean±SD age of the participants was 32.42 ± 5.20 in the calcium and 30.10 ± 6.08 years in the placebo groups (P = 0.27). The mean levels of AMH did not differ significantly between the two groups (P = 0.53). The duration of infertility did not differ significantly between the calcium and placebo groups (P = 0.53; Table 1).

The two groups were not significantly different in terms of their mean BMI (P = 0.86) or the distribution of infertility causes. (Tables 1 and 2). Endometriosis was detected in 14% of the calcium group and 25% of the placebo group (P = 0.53). Male factor infertility was present in 7% of the calcium group and 37% of the placebo group (P = 0.07). The corresponding rates of tubal factor infertility were 7% and 12% (P = 0.67). Unexplained infertility was found in 7% of the

| Variable                | Calcium group mean ±SD | Placebo group mean ±SD | P Value |
|-------------------------|-------------------------|------------------------|---------|
| Age                     | 32.42 ± 5.20            | 30.10 ± 6.08           | 0.27    |
| BMI                     | 26.18 ± 4.01            | 25.86 ± 4.27           | 0.86    |
| AMH                     | 7.91 ± 7.61             | 5.90 ± 4.78            | 0.53    |
| Duration of infertility | 4.68 ± 2.70             | 5.77 ± 5.93            | 0.53    |
| Serum estradiol level   | 3047.10 ± 760.86        | 3067.27 ± 762.11       | 0.94    |
calcium group and 0% of the placebo group (P = 0.43). Moreover, 71% of the calcium group and 37% of the placebo group had polycystic ovary syndrome (P = 0.11; Table 2).

Metformin was taken by 47% of the calcium group and 18% of the placebo group (P > 0.05). The mean serum estradiol levels were 3047.10 in the calcium and 3067.27 pg/ml in the placebo groups (P = 0.94; Tables 1 and 2).

The two groups had no significant differences in terms of their oocyte or grade A, B or C embryo counts (P = 0.62 and P > 0.05, respectively; Table 3; Figure 1). The embryo transfer rate was 28% in the calcium group and 63% in the placebo group (P = 0.055). The clinical pregnancy rate was 33% in the calcium group and 28% in the placebo group (P = 0.85; Table 4; Figure 2).

The two groups had no significant differences in terms of the frequency of OHSS symptoms. While 14% of the calcium group and 3% of the placebo group complained of nausea (P = 0.18), none of the participants reported vomiting. Abdominal pain was present in 42% of the patients in the calcium group and 0% of the placebo group (P = 0.43).

| Variables               | Calcium group | Placebo group | P Value |
|-------------------------|---------------|---------------|---------|
| Male factor             | 7%            | 37%           | 0.07    |
| Tubal                   | 7%            | 12%           | 0.67    |
| Unexplained             | 7%            | 0%            | 0.43    |
| Endometriosis           | 14%           | 25%           | 0.53    |
| PCO                     | 71%           | 37%           | 0.11    |
| Metformin consumption   | 47%           | 18%           | 0.10    |

Figure 1. A comparison of oocyte count and embryo transfer rate between calcium and placebo groups.

| Variables               | Calcium group mean ±SD | Placebo group Mean ±SD | P Value |
|-------------------------|-------------------------|-------------------------|---------|
| Oocyte count            | 13.33 ± 6.08            | 14.09 ± 2.46            | 0.62    |
| Embryo count            | 9.43 ± 5.98             | 10.00 ± 1.85            | 0.73    |
| Embryo grade A          | 8.00 ± 5.57             | 7.37 ± 4.53             | 0.78    |
| Embryo grade B          | 0.37 ± 0.80             | 1.50 ± 3.50             | 0.39    |
| Embryo grade C          | 1.00 ± 1.89             | 1.25 ± 1.58             | 0.75    |
group and 36% of those in the placebo group (P = 0.72). Abdominal distention was reported by 4% of the calcium group and none of the patients in the placebo group (P = 0.46; Table 5).

The two groups were also compared in terms of OHSS signs. The level of fluid accumulation was estimated based on their transvagal ultrasound and classified as mild, moderate or severe. Mild fluid collection was observed in 38% of the patients in the calcium group and 45% of those in the placebo group (P = 0.68%). The rates were respectively 57% and 54% for moderate fluid accumulation (P = 0.88) and 4% and 0% for severe fluid accumulation (P = 0.46; Table 5; Figure 3).

The mean hematocrit levels were 39% in the calcium group and 40.36% in the placebo group (P = 0.25). The mean White Blood Cell (WBC) count was not significantly different between the two groups (P = 0.22; Table 6).

| Variables               | Calcium group | Placebo group | P Value |
|-------------------------|---------------|---------------|---------|
| Embryo transfer rate    | 28%           | 63%           | 0.055   |
| Clinical pregnancy      | 33%           | 28%           | 0.85    |

**Table 4. A comparison of clinical pregnancy and embryo transfer rate between calcium and placebo groups**

| Variables               | Calcium group | Placebo group | P Value |
|-------------------------|---------------|---------------|---------|
| Nausea                  | 14%           | 0%            | 0.18    |
| Abdominal pain          | 42%           | 36%           | 0.72    |
| Mild abdominal pain     | 19%           | 9%            | 0.46    |
| Moderate abdominal pain | 9%            | 27%           | 0.18    |
| Severe abdominal pain   | 4%            | 0%            | 0.46    |
| Distention              | 4%            | 0%            | 0.46    |
| Mild fluid              | 28%           | 18%           | 0.51    |
| Moderate fluid          | 52%           | 54%           | 0.90    |
| Severe fluid            | 4%            | 0%            | 0.46    |
| Mild OHSS               | 38%           | 45%           | 0.68    |
| Moderate OHSS           | 57%           | 54%           | 0.88    |
| Severe OHSS             | 4%            | 0%            | 0.46    |

**Table 5. A comparison some symptoms of OHSS and Prevalence of mild, moderate and severe OHSS between two groups**
The calcium and placebo groups (38%) had no significant differences in terms of the frequency of mild, moderate and severe OHSS symptoms (38% vs. 45%, P = 0.68; 57% vs. 54%, P = 0.88; and 4% vs. 0%, P = 0.46, respectively; Table 5).

5. Discussion
This study compared the effectiveness of oral calcium and placebo in the prevention of moderate to severe OHSS in patients at risk of OHSS due to ART. The findings showed no significant differences in oocyte and grade A, B and C embryo counts between the two groups. Moreover, the clinical pregnancy rate and the frequency of OHSS symptoms were not significantly different between the two groups (P = 0.85 and P > 0.05, respectively). The two groups were also compared in terms of OHSS signs. No significant differences were observed in their rates of fluid accumulation, mean hematocrit levels or mean WBC count. Furthermore, the frequencies of mild, moderate and severe OHSS were not significantly different between the two groups.

El-Khayat and Elsadek (2015) compared the effects of 10-ml intravenous calcium gluconate 10% in 200-ml normal saline and placebo (in normal saline) on the date of the ovum pick-up and one, two and three days later and concluded that intravenous calcium decreases the risk of OHSS without affecting pregnancy rates. The oral dose of calcium carbonate administered in the present study (500 mg BID), however, was not effective in the prevention of moderate to severe OHSS. Lower calcium absorption through the oral route (as a result of its gastrointestinal absorption) can justify the observed inconsistency between the two studies. El-Khayat and Elsadek (2015) found no significant differences in clinical pregnancy rates between their calcium and placebo groups.

In a retrospective study, Gurgan et al. (2011) reported that intravenous calcium infusion causes a significantly lower rate of OHSS development in patients with polycystic ovary syndrome at a high risk of OHSS. The patients received either intravenous calcium gluconate for OHSS prevention (n = 84) or no medications for the prevention of the condition (n = 371). The patients were included if they had more than 14 leading follicles larger than 10 mm and a serum estradiol level higher than 3,000 pg/mL at the end of the ovulation induction with oral contraceptives plus long
luteal down-regulation protocol. In the present study, the patients had an antagonist protocol for ART and received oral calcium carbonate (500 mg/day) for five days. The insufficient dose of oral calcium in the present study might explain the observed discrepancy.

Saad and Mohamed (2017) studied 200 women at a high risk of developing OHSS in two groups. Group A received calcium dobesilate 1 cap/8 h (500 mg) orally from the day of hCG injection for 21 days. Group B received cabergoline 1 tab/day (0.5 mg) orally from the day of hCG injection for eight days. The patients were assessed weekly up to eight weeks. The rate of OHSS development was significantly lower in the calcium dobesilate recipients than in the cabergoline group (12% vs. 28%, P = 0.005). Moreover, the frequency of severe OHSS was significantly lower following calcium dobesilate administration compared to cabergoline administration (2% vs. 13%, P = 0.003). The clinical pregnancy and miscarriage rates were not significantly different between the two groups. In the present study, the clinical pregnancy rate was not significantly different between the calcium carbonate and placebo groups (P = 0.85), but the administration of calcium carbonate tabs (500 mg BID) for five days was not significantly more effective than placebo in terms of OHSS prevention. The lower dose and shorter period of treatment in the present study may justify this inconsistency. The study by Saad and Mohamed (2017) was one of the first studies to use calcium dobesilate for preventing OHSS, and studies on the role of oral calcium in OHSS prevention are rare.

Since oral calcium is an easy-to-use method with limited side-effects, we recommend further studies on its effects in OHSS prevention in high-risk patients. The researchers plan to design another study with an adjusted dose and duration of oral calcium administration to better evaluate the effects of oral calcium on OHSS prevention.

6. Conclusion

Ovarian hyperstimulation syndrome (OHSS) is a serious complication of ART. Some studies show that intravenous calcium infusion decreases the risk of OHSS in high-risk patients. Oral calcium carbonate is a cheap and easy-to-use drug with no/minor side-effects; therefore, this study was designed to identify the role of oral calcium in OHSS prevention in high-risk patients. The findings showed that the administration of oral calcium carbonate at 500-mg BID doses from the puncture date for five days is not effective in the prevention of OHSS in high-risk patients. Further studies are therefore recommended to be conducted with an adjusted dose and duration of oral calcium administration to better evaluate the effects of oral calcium on OHSS prevention in high-risk patients.

Acknowledgements
The authors would like to express their gratitude to the patients and the infertility department staff of Tehran University of Medical Sciences for all their help.

Funding
The authors received no direct funding for this research.

Competing Interests
The authors declare no competing interests.

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Conflicts of Interest
None of the authors declare any conflicts of interest.

Citation information
Cite this article as: The effects of oral calcium on the prevention of moderate to severe ovarian hyperstimulation syndrome in high-risk patients: A placebo-controlled study, Zahra Rezaei, Zahra Dehbashi, Fatemehsadat Hoseini & Hoora Amuzegar, Cogent Biology (2019), 5: 1668212.

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