ETIOLOGY OF OHSS AND USE OF DOPAMINE AGONISTS

+ VASCULAR ENDOTHELIAL GROWTH FACTOR AND OVARIAN HYPERSTIMULATION SYNDROME

- OHSS
  - Increased vascular permeability (VP)
  - Shift of fluid from the intravascular to the third space
    - Hemoconcentration
    - abdominal distension

CAUSE?

- hCG has no direct vasoactive properties
- Cytokines and growth factors (IL-2, IL-6, IL-8, IL-10, IL-18, vascular endothelial growth factor [VEGF]), histamine, prolactin, prostaglandins, and reninangiotensin

VEGF IS CRUCIAL FOR THE DEVELOPMENT OF THE SYNDROME

- 1. Its expression is increased by hCG and is higher in cases of OHSS.
- 2. Its effect on vascular permeability is clear and strong.
- 3. The inhibition of its effect in hyperstimulated women blocks or attenuates the clinical manifestations of OHSS.

THE IMPACT OF HCG ON VEGF EXPRESSION

- After hCG administration
  - VEGF mRNA, VEGF receptor-2 (VEGFR-2) mRNA, and VP reach their peak in only 48 hours
- VEGF and VEGFR-2 proteins increased in the granulosa and endothelial cells of ovarian follicles after hCG administration
- hCG stimulates VEGF mRNA expression of granulosa
- endothelium responds to hCG by releasing VEGF and increasing the amount of VEGFR-2

THE ROLE OF VEGF IN INCREASED VP SEEN IN OHSS AND THE FFECT OF ITS INHIBITION

- Some studies showed
  - In humans, VEGF–VEGFR binding strongly induces angiogenesis and increases VP in the ovary
  - The binding of VEGF to its transmembrane receptor VEGFR-2 determines the phosphorylation of the receptor intracellular domains -> critical step leading to increased VP

THE ROLE OF VEGF IN INCREASED VP SEEN IN OHSS AND THE FFECT OF ITS INHIBITION

- VEGF increased VP in OHSS
  - in vitro study
  - recombinant human VEGF antiserum significantly decreased the vascular permeability effect of ascitic fluid from hyperstimulated women

THE ROLE OF VEGF IN INCREASED VP SEEN IN OHSS AND THE FFECT OF ITS INHIBITION

- Another in vitro model of VP showed that follicular fluid (FF) from
  - women with a high ovarian response to gonadotropin stimulation
    - Stronger endothelial cell permeability effect
  - 98% of this effect was reversed by anti-VEGF antibody
  - Serum levels of VEGF are also associated with the probability of developing OHSS and with its clinical picture capable of preventing VP

THE ROLE OF VEGF IN INCREASED VP SEEN IN OHSS AND THE FFECT OF ITS INHIBITION

- In rodents
  - SU5416 –a synthetic compound developed to inhibit angiogenesis in different cancers
    - by avoiding the initial VEGF–dependent VEGFR–2 phosphorylation and subsequent downstream signaling
    - inhibit the increased VP induced by hCG after ovarian stimulation in an OHSS model
    - This was the first in vivo study to show a cause–and–effect relationship between increased VEGF expression and capillary permeability in OHSS

THE ROLE OF VEGF IN INCREASED VP SEEN IN OHSS AND THE FFECT OF ITS INHIBITION

- However, because of its side effect profile (thromboembolism, vomiting) and to the possibility that it might interfere with early pregnancy development by blocking implantation-related ovarian and uterine angiogenesis, SU5416 cannot be used in humans to treat OHSS (27–35).

DOPAMINE AGONISTS AND OHSS

- The first report to indicate that the use of dopamine might have an impact on OHSS pathophysiology dates back to 1992
  - IV dopamine infusion improved urinary output and overall symptoms in seven critically ill OHSS patients after.

DOPAMINE AGONISTS AND OHSS

- In another study to treat mildly hyperprolactinemic women with polycystic ovary syndrome:
  - group A
    - 18 women, normalized PRL levels with the use of cabergoline (Cb2) before ovarian stimulation for intrauterine insemination
  - group B
    - 26 women without dopamine agonist treatment.

DOPAMINE AGONISTS AND OHSS

- Result:
  - The number of follicles and final E2 levels were both significantly lower in group A
  - The incidence of cycle cancellation as a result of mild ovarian hyperstimulation syndrome was also higher in group B (6.2% vs. 2.4%)
  - but this difference did not reach statistical significance.
- The authors concluded that the stimulation of dopaminergic activity was associated with a reduction in ovarian follicular activity.

THE ASSOCIATION BETWEEN DOPAMINE AGONISTS AND VEGF

- Dopamine ligand activation
  - led to the internalization of VEGFR-2
  - capable of blocking downstream signaling of the VEGF ligand–receptor pathway

THE ASSOCIATION BETWEEN DOPAMINE AGONISTS AND VEGF

- Cb2 first used in the clinical context of OHSS (case report)
  - First group
    - 20 patients at risk of hyperstimulation
    - Cb2 was initiated the evening after egg pick-up at a dose of 1 mg every 48 hours
  - Second group
    - 10 severely hyperstimulated hospitalized pregnant women
    - Cb2 was initiated after 24-48 hours of dopamine infusion
  - The authors reported the absence of OHSS in the group of patients at risk and a prompt improvement in the hospitalized patients

THE ASSOCIATION BETWEEN DOPAMINE AGONISTS AND VEGF

- Relationship between VEGF and dopamine was reinforced
  - (by the study of ovarian gene expression in hyperstimulated rats)
- Among 14,000 genes, only 8 were significantly down-regulated
  - tyrosine hydroxylase
    - responsible for dopamine synthesis
  - High VEGF activity in OHSS was therefore linked with reduced dopamine production.

THE ASSOCIATION BETWEEN DOPAMINE AGONISTS AND VEGF

- Does DA have antiangiogenic effect?
  - detrimental for pregnancy achievement and development
- In the oncology model
  - No antiangiogenic activity is observed with these doses
  - high level VEGFR-2–dependent vascular activity such as corpus luteum physiology or gestation are not affected by such drugs

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Rodents
  - low doses of Dpr2–activating drugs to decreasing VEGF–induced VP seen in OHSS without affecting angiogenesis
    - first tested in rodents
  - In an OHSS rat model, low–dose Cb2 reversed VP without affecting luteal activity
    - ascites was significantly reduced
    - serum progesterone levels were not altered
    - luteal apoptosis was not increased

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Cb2 administration did not affect VEGF/VEGFR-2 ovarian mRNA levels
- But phosphorylation of VEGFR-2 was reduced by 42% compared with controls.
- These data indicated that reduced phosphorylation of specific tyrosine sites of VEGFR-2 could segregate VP and angiogenic effects.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- The phosphorylation of the tyrosine sites in the transmembrane and C-terminal regions of the receptor are known to induce subsequent VEGFR-2 downstream signaling
- Studies in Dpr2 knockout models show that VEGFR-2 phosphorylation, VP, and angiogenesis are increased tenfold in the absence of inhibition exerted by the Dp-Dpr2 ligand–receptor complex and cannot be reversed by the administration of DA (54).

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Humans
  - in vitro studies corroborate the association between low dopaminergic tone and increased VEGF activity
    - In women with polycystic ovary syndrome
    - lower density of Dpr2 in the granulosa layer of small follicles and in the theca of antral follicles

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Interestingly, the authors found that Cb2 inhibited the production of VEGF by cultured granulosa cells exposed to hCG, which indicates that reduced VEGFR-2 phosphorylation may not be the sole mechanism of action through which DA interferes with VEGF activity.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- However, such inhibition was less effective in cells from patients with polycystic ovary syndrome. These cells also secreted lesser amounts of dopamine.
- Polycystic ovaries had higher stromal vascularization than controls, which is in accordance with previous studies that showed higher VEGF expression in their theca and stroma (56, 57).

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- First RCT on the use of DA to prevent OHSS
  - In oocyte donors at risk of developing the syndrome
    - >25 preovulatory follicles
    - serum estradiol >3000 pg/mL on the day of hCG administration
  - Cb2 was used in a dose of 5–10 mg/kg per day
    - to block prolactin secretion without interfering with ovarian function

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Result:
  - Prophylactic Cb2 was associated with a significant reduction in the incidence of symptoms and signs of moderate/severe OHSS
  - more than 75% of women in the treatment group (N ¼ 63) were free of these findings, compared with only 15% in the placebo group (N ¼ 57)
  - Another important finding of this study was the confirmation of the presence of Dpr2 in human granulosa–lutea l cells.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Ovarian vascular permeability (quantitative dynamic contrastenhanced MRI) was increased in the placebo group after hCG administration.
- Infertile women at risk of OHSS given Cb2 were found to have fertilization, implantation, and pregnancy rates similar to those of controls matched for age and embryo number and quality.
- Ongoing and full-term pregnancies were also similar in both groups.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- No major perinatal problems were detected in treated cases.
- Even early pregnancy Cb2 administration does not seem to be harmful
  - the use of up to 7 mg/wk
  - not associated with increased frequencies of miscarriages or major congenital malformations

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- There is another RCT to evaluate the use of Cb2 in patients at risk of OHSS
  - 166 patients were randomized into two groups
    - group A (n ¼ 83) received 21 days of 0.5 mg of daily Cb2, beginning the day of oocyte retrieval
      - early-onset OHSS was significantly reduced in group A (0% vs. 15%)
    - group B (n ¼ 83) received no medication
    - No significant differences were observed in the incidence of late-onset OHSS
    - Obstetric outcome also did not differ between groups

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- A meta-analysis was published in 2010 on the impact of Cb2 on the incidence and severity of OHSS
  - This review included the two RCTs mentioned above and two other studies that were congress presentations but, to our knowledge, have not been published as full papers.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- 570 women were studied.
- Cb2 dose was 0.5 mg in three studies and 0.25 mg in one study.
- Starting time varied from the day of hCG to the day following retrieval, and the duration varied from 4 to 21 days.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Result:
  - The incidence of OHSS was significantly reduced by the use of Cb2 (odds ratio [OR] ¼ 0.41, 95% confidence interval [CI] ¼ 0.25–0.66)
  - Although the incidence of severe forms was lower in women who received Cb2 (OR ¼ 0.50, 95% CI¼ 0.20–1.26), the difference was not significant, because of the low incidence of severe forms of OHSS.
  - No differences between treatment and placebo groups were observed with regard to clinical pregnancy and miscarriage rates.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Although there is no evidence of long-term complications with the low dose and short-term regimens used to prevent OHSS
  - long-term use of Cb2 in patients with prolactinomas and Parkinson's disease
    - associated with a low incidence of fibrotic changes and dysfunction in cardiac valves
  - The stimulation of the serotonin receptor subtype 5-HT2b in valvular cardiac tissue may lead to proliferation of fibroblasts

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Quinagolide
  - non-ergot-derived Dpr2 agonist lacking an effect on the serotonin receptor
  - not seem to be associated with an increased prevalence of cardiac complications

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- One RCT on the effect of the DA quinagolide on OHSS prevention
  - 182 IVF patients at risk of OHSS
  - randomized to either placebo or three different doses of quinagolide (50, 100, and 200 mg/d), from the day of hCG administration until the day of the pregnancy test

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Significant reduction in the incidence of OHSS was observed with all quinagolide doses
- Sonographic evidence of ascites was also significantly reduced (OR ¼ 0.33, 95% CI ¼ 0.13–0.89)
- Considering only severe OHSS, the OR for treated patients was 0.13
  - but the low sample size led to a 95% CI of 0.00–1.67 (no significant difference)

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- In pregnancy, clinical pregnancy, implantation, ongoing pregnancy, and live birth rates
  - No significant differences between groups
- Higher doses of quinagolide were associated with poor tolerability because of gastrointestinal and central nervous system symptoms

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- DA side effects
  - Studies with 0.5 mg daily doses of Cb2 report good tolerability
  - Higher dose of quinagolide used to prevent OHSS was associated with 27% of discontinuation of treatment
    - Reduced gastrointestinal tonus (nausea and vomiting)
    - Dizziness
    - Somnolence

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Care must be taken in the follow-up of patients who use any DA, especially in cases in which progesterone is given for luteal support and further impairs bowel motility.
- We are aware of severe constipation in two patients receiving IM progesterone.
- Patients being treated with DA should be forewarned to institute preventive measures if they notice any incipient

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Bromocriptine, the longest known DA used to treat hyperprolactinemia, was only recently examined for the prevention of OHSS.
- Forty patients at risk of developing the syndrome at the end of ovarian stimulation for IVF received a daily rectal dose of 2.5 mg for 16 days, beginning the day of oocyte retrieval (72).

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- A historical control group of 44 age- and BMI-matched patients stimulated for IVF was used.
- The strength of ovarian response was similar in both groups.
- The incidence of early-onset and moderate OHSS was significantly lower in the study group..

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- The incidence of fresh Ets performed in the study group was significantly higher, because no transfer was deferred (100% vs. 54.5%).
- No significant differences were observed in clinical pregnancy rate and pregnancy outcome. The authors reported good tolerability of the medication in all 40 patients.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Another group performed an uncontrolled study on use of the same dose of bromocriptine in 44 patients at risk of OHSS after ovarian stimulation for IVF, also starting the day of oocyte retrieval (73).
- The oral route was chosen. Severe nausea and vomiting after the initiation of the DA occurred in two patients (4.8%).

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Alternative approaches were proposed with DA to control established OHSS.
- A case was reported in which an IVF patient at risk for OHSS started Cb2 0.5 mg daily the day of hCG administration, and 4 days later the dose was raised to 1.0 mg daily because of a diagnosis of moderate OHSS with abdominal distention, ascites, and hemoconcentration (hematocrit 42%) (74).

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Stabilization of the clinical condition was achieved 3 days after the Cb2 dose was raised, ascites did not progress, and hematocrit decreased to 38%.
- Embryo transfer was performed on day 5 of embryo development and a single pregnancy was achieved. The 1.0–mg daily dose of Cb2 was maintained until 14 days after ET.
- The pregnancy developed well and a healthy boy was delivered at term after an uneventful gestation.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Another group described the association of Cb2 and GnRH antagonists in the treatment of four consecutive cases of OHSS that presented between egg pick-up and the scheduled day for ET (75).
- Embryos were frozen and the patients received 0.5 mg of oral Cb2 daily for 7 days and two doses of 250 mg of Ganirelix SC with a 24-hour interval.

TARGETING VEGF-INDUCED INCREASE IN VASCULAR PERMEABILITY WITH DA

- Moderate and severe OHSS promptly improved, with no need for hospitalization.
- All of them were symptom free by 1 week after the initiation of treatment.

CONCLUSIONS

- The VEGF molecule is crucial for the increased vascular permeability that determines OHSS.
- Dopamine agonists are capable of selectively inhibiting VEGF-induced vascular permeability without interfering with angiogenesis, through mechanisms that are not completely clarified.
- Reduced VEGFR-2 phosphorylation seems to underlie this effect.

CONCLUSIONS

- The preventive use of dopamine agonists reduces the incidence of OHSS in women at risk after ovarian stimulation for IVF.
- The statistical evidence of their effect on the prevention of severe forms of the syndrome is not as clear as in the case of moderate forms.

CONCLUSIONS

- The use of dopamine agonists does not interfere with the outcome of IVF cycles.
- The occurrence of obstetric or neonatal complications is not different from those seen in control groups.

CONCLUSIONS

- The oral administration of cabergoline is the best studied DA regimen in the prevention of OHSS. High-dose quinagolide is associated with a high incidence of intolerable side effects.
- Oral bromocriptine can also be occasionally associated with severe gastric discomfort, although less frequently than with quinagoline.
- Rectal bromocriptine deserves further

CONCLUSIONS

- Although published data suggest that dopamine agonists also improve the clinical evolution of established OHSS, no randomized controlled trials have been published to confirm their effectiveness.
- The use of dopamine agonists may be associated with other strategies to prevent or control OHSS, such as GnRH antagonists, in order to improve its efficacy.

GUIDELINES FOR USE OF DA TO PREVENT OHSS

- DA use can lower the incidence of early-onset OHSS
- No severe complications have been reported with the short-term drug regimens used. Still, until the pharmaceutical industry and the regulation and supervision national agencies recognize this specific indication, it might be advisable to require an informed consent from patients to whom DA are prescribed for this purpose.

GUIDELINES FOR USE OF DA TO PREVENT OHSS

- The use of DA should be considered only in patients at risk of OHSS.
- Significant OHSS risk at the end of ovarian stimulation
  - the presence of one or more of the following findings: >20 growing follicles (mean diameter R12 mm)
  - serum E2 >3,000 pg/mL the day of hCG administration;
  - presence of incipient ascites during the final days of ovarian stimulation.
- A history of OHSS with a previous stimulation may indicate DA use even with less evident signs of a strong ovarian

GUIDELINES FOR USE OF DA TO PREVENT OHSS

- Oral cabergoline must be initiated the day of hCG administration and ideally a few hours before the injection.
- Knowledge on the pathophysiology of the syndrome indicates it is most effective to make the DA available before the rise in VEGF production and release triggered by hCG.
- At present, the best known effective regimen is 0.5 mg daily for 8 days. Rectal bromocriptine at a daily dose of 2.5 mg for 16 days may be a reasonable alternative.