The Ovarian Hyperstimulation Syndrome (OHSS) was first described in 1943 by Ryder et al. as a loss of control over the intended therapeutic stimulation of the ovary. In 1957, the first case of OHSS was reported and it immediately became a potential complication associated with assisted reproductive techniques (ART), particularly with controlled ovarian stimulation (COS). Nowadays, it is considered the major risk related to ART, not just multiple pregnancies (1). In 2012, OHSS was reported in 0.4% European women undergoing a cycle of ovulation stimulation. The central factor in triggering OHSS is an increase in intra-abdominal pressure, either endogenous or exogenous, and it is because of the different source of this hormone that becomes its principal classification (Table 1): iatrogenic OHSS, spontaneous OHSS, and prophylactic OHSS.

In both cases, it consists in a self-limiting syndrome in which the symptoms decline 10-14 days after its debut. The first symptoms are abdominal discomfort and distention, nausea, vomiting, and/or diarrhea. At that point, vascular permeability increases resulting in protein-rich fluid from the intravascular space to the peritoneal surfaces, being this characteristic the cardinal feature of OHSS. The symptoms which follow this event depend on the severity of the syndrome (Figure 1/2).

![Figure 1. OHSS and the pathophysiology involved.](image1)

Even though the main mediators of the syndrome are known, today many aspects of OHSS aetiology are unclear. It has not been elucidated why only a group of patients develop this life-threatening syndrome.

### Relevant results in BASIC RESEARCH

#### Individual susceptibility in high-risk patients

High-risk OHSS patient’s determination previous to ovarian stimulation has been the most useful tool in the prevention of the syndrome at the clinical practice.

- **Risk factors:** Young women (20-35), low BMI, PCOS, 7 am fertilisations, etc.
- **Indicative OHSS:**
  - Sporadic OHSS
  - Spontaneous OHSS
  - Prophylactic OHSS

Nevertheless, the long-standing problem has been that, in some cases:
- Patients considered at high-risk for OHSS have not developed the syndrome
- Patients not considered at high-risk for OHSS have developed the syndrome

Recent studies have concluded that the responsible for this inaccuracy are the subtypes VEGF receptors (vEGFR) (Figure 2).

These receptors bind to VEGF and/or PlGF by preventing the interaction with its receptor VEGFR-2 (4). Thus, the vascular permeability remains stable.

#### FSH mutations and sporadic OHSS

During pregnancy hCG reaches a maximum concentration about 8-16 weeks, which can cross-activate mutated FSHR (Figure 3).

FSH promotes VEGF and VEGF2 receptor binding and synthesis, which in turn releases its main isoforms in the corpus luteum (Figure 4).

Vascular permeability increases in the corpus luteum, thereby causing the development of sporadic OHSS.

#### Clinical approach

Even though FSH mutations provided, for the first time, an explanation about the aetiology of spontaneous OHSS, as there are sporadic cases in pregnant women without any FSH mutations, the standardised screening of allelic variants in all pregnant women is not currently considered.

### Genetic aetiology of OHSS

The multiple reported cases of sporadic OHSS in members of the same family sparked the interest in the research of a possible genetic aetiology of the syndrome. In 2003, Jousset and others at this conference confirmed this hypothesis by detecting activating polymorphisms in FSHR gene. Over the years, many investigators have identified other polymorphisms sequencing the same gene and, in all cases, it has been demonstrated that FSHR mutations broaden the specificity of this receptor (Table 2).

Then, it can be activated either by FSH or hCG. In some cases it can also be activated by TSH as a consequence of the homozygosity between all these hormones (Figure 3/4).

### OHSS and ovarian cancer

A recent study published in 2013 suggested the possible connection between OHSS and a higher risk of ovarian cancer. This speculation was a result of studies which established a relationship between:

- Ovarian and ovarian cancer
- Ovarian stimulation and ovarian cancer

#### Clinical research limitation

All results coming from OHSS clinical research are considered unreliable because of low quality and as a consequence of the lack of a standardised definition of high-risk patients, lack of an uniform classification of OHSS severity, lack of standardised protocols used, etc.

#### Conclusions

Summarizing the results and discussions of this literature review it can be concluded that:

- Currently, OHSS is considered one of the highest risks associated with ART and is described as an idiosyncratic syndrome because the aetiology has not been completely elucidated.
- Actual research can be divided in a basic and a clinical side, each one with different aims.
- Among high-risk patients there is an individual susceptibility determined by vEGFR.
- There are genetic cues of OHSS in pregnancy due to FSHR mutations, which broaden its specificity.
- The detection of carrier women is not contemplated by physicians.
- In sporadic OHSS the allelic variant Anom is useful as a predictive factor.
- It has been suggested that dopamine agonists reduce incidence without affecting pregnancy rate and that there is no causative association between OHSS and ovarian cancer.
- It is necessary to standardize the definition, classification and treatment protocols in clinical research.

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**Table 2. FSHR allele variants and their functional consequence.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Mutation</th>
<th>Location in FSHR</th>
<th>Cumulative activity</th>
<th>FSH receptor expression</th>
<th>NGS response</th>
<th>TSH response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vannier et al. [2003]</td>
<td>T1448C</td>
<td>rs2820397</td>
<td>Exon 18, JH locus III</td>
<td>TSH domain</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Emre et al. [2003]</td>
<td>T1678G</td>
<td>rs2820370</td>
<td>Exon 18, JH locus IV</td>
<td>TSH domain</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Mortezl et al. [2004]</td>
<td>T1679A</td>
<td>rs12199063</td>
<td>Exon 18, JH locus III</td>
<td>TSH domain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>De Laouer et al. [2006]</td>
<td>T1679A</td>
<td>rs12199064</td>
<td>Exon 18, JH locus III</td>
<td>TSH domain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>De Laouer et al. [2008]</td>
<td>T1679A</td>
<td>rs12199065</td>
<td>Exon 18, JH locus III</td>
<td>TSH domain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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**Figure 1. OHSS and the pathophysiology involved.**

**Figure 2. Mutated FSHR can be activated by endogenous hCG triggering sporadic OHSS of the pregnant woman.**

**Figure 3. Mutated FSHR can be activated by endogenous hCG triggering sporadic OHSS of the pregnant woman.**

**Figure 4. Active FSHR stimulates massive follicular recruitment and enlargement.**

**Figure 5. Mutated FSHR can be activated by endogenous hCG triggering sporadic OHSS of the pregnant woman.**

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**REFERENCES**


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**Clinical research:**

- Prevention/Treatment strategies
- Ovarian cancer risk analysis
- Short/long-term consequences analysis

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**Aims and methodology**

**Basic research:**

- Syndrome aetiology

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**Current status of OHSS**

- The aims of this review are:
  - To show the most relevant results of OHSS basic research. Issues related to individual susceptibility and genetic aetiology.
  - To show the focus of OHSS recent clinical research.

Scientific literature has been searched on PubMed database prioritizing those reviews and meta-analysis published in the last 5-10 years using keywords such as ‘OHSS’ (AND)(‘pathology’, ‘VEGF’, ‘genetics’, ‘treatment’, ‘cancer’).