

# Hydrosalpinx Functional Surgery or Salpingectomy? The Importance of Hydrosalpinx Fluid in Assisted Reproductive Technologies

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## ABSTRACT

The first IVF baby, Louise Brown, was born in a natural cycle IVF of a woman who had bilateral tubal block making IVF the only option for having a child. The last 3 decades has seen astounding progress in the field of ART. Today thanks to ART, tubal disease and tubal factor infertility is easily overcome. The accepted theory today is that the hydrosalpinx fluid plays a causative role in the reduced pregnancy rate with ART. It is well known that the success of ART for patients with tubal disease with hydrosalpinx is reduced by half compared with patients without hydrosalpinx. Ideal would be removal of a hydrosalpinx by laparoscopic salpingectomy to improve pregnancy rates. However in some cases this is not feasible due to dense pelvic adhesions making access difficult. In such cases it is recommended that even de-linking the tube from the uterus would help in improving the ART outcome. There is suggestion that sonographically visible hydrosalpinges and those affected bilaterally have a poorer prognosis than those seen incidentally at laparoscopy. While there is clinical evidence supporting the causative role of the fluid itself, there is a lack of knowledge as to how the fluid exerts its negative effects. It is generally believed that the fluid holds a key position in impairing implantation potential. The aim of this review is to highlight the importance of identifying hydrosalpinges and its association with reduced fertility outcome using assisted reproductive technologies. Here we have discussed the different options available for the same, and highlighted the current modes of treatment.

**Key words:** Hydrosalpinx, hydrosalpinx fluid, ART, pregnancy outcome

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## INTRODUCTION

When the first IVF baby, Louise Brown, was born in 1978, *in-vitro* Fertilization (IVF) was still an experimental technique. She was born in a natural cycle IVF of a woman who had bilateral tubal block, making IVF the only option for having a child. Prior to this, there was no hope for women with tubal factor infertility

to ever conceive their own child. The results with tubal reconstructive surgery were unsatisfactory and had a high incidence of ectopic pregnancies. The last three decades has seen astounding progress in the field of Assisted Reproductive Technologies (ART). Today, thanks to advances in modern medicine, infertility treatment has become almost a routine procedure. With the advent of better quality ovulation induction drugs and increasing availability and accessibility of ART, there have been more than one-and-a-half million babies born with the help of ART. The happiness this has brought to families all over the world is incalculable. Today, thanks to ART, tubal disease and tubal factor infertility is easily overcome. The aim of this review is to highlight the importance of

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identifying hydrosalpinges and its association with reduced fertility outcome using ART. The ultimate aim of ART is to improve the take-home baby rate, and dealing with hydrosalpinx prior to ART is important. The literature review is done with the help of MEDLINE (1966 to November 2008), the Cochrane Library databases, and journal search, for the different options available for the same, and highlights of the current modes of treatment.

### HYDROSALPINX AND ART OUTCOME

The accepted theory today is that the hydrosalpinx fluid plays a causative role in the reduced pregnancy rate with ART. It is well known that the success of ART for women with tubal disease with hydrosalpinx is reduced by half when compared with women without hydrosalpinx. During the past decade, the influence of the presence of hydrosalpinx on IVF success rates has been an issue of debate and research. Many retrospective studies have shown an impaired outcome of IVF in the presence of hydrosalpinx, and the meta-analyses has demonstrated that the probability of achieving a pregnancy in the presence of hydrosalpinx is reduced by half and even if pregnancy is achieved the incidence of spontaneous abortion is doubled.<sup>[1-3]</sup> Hence, any surgical intervention blocking the communication between the tube and the uterus would remove the leakage of the hydrosalpinx fluid and restore pregnancy rates. The ideal solution would be the removal of the hydrosalpinx by laparoscopic salpingectomy, to improve pregnancy rates.<sup>[4-6]</sup> However, in some cases this is not feasible due to dense pelvic adhesions making access difficult. In such cases it is recommended that even de-linking the tube from the uterus would help in improving the ART outcome.<sup>[7]</sup>

The results of prospective randomized studies on salpingectomy in women with hydrosalpinges are now forthcoming and greatly assist the debate on whether or not IVF will benefit from salpingectomy. In a study by Strandell *et al.*<sup>[5]</sup> the diagnosis of hydrosalpinx was made by a previous hysterosalpingography (HSG) or diagnostic laparoscopy, at which time reconstructive surgery had been rejected. The patients were divided into groups, IVF after salpingectomy and IVF cycle without removing the hydrosalpinges. The authors reported the outcome of the first IVF cycle and concluded that salpingectomy can be recommended for women with hydrosalpinges, especially those enlarged enough to be visible on ultrasound and in particular for those affected bilaterally.<sup>[5]</sup> These studies have resulted in the Cochrane library recommendation of salpingectomy for hydrosalpinges.<sup>[8,9]</sup> Although there is clinical evidence supporting the causative role of the

fluid itself, there is a lack of knowledge as to how the fluid exerts its negative effects. It is generally believed that the fluid holds a key position in impairing the implantation potential.

### SONOGRAPHICALLY VISIBLE HYDROSALPINX — IS IT A NEW CLINICAL ENTITY?

The hydrosalpinx that is visible on transvaginal sonography has been proposed as a new clinical entity by de Wit *et al.* in 1998,<sup>[10]</sup> although the diagnostic and pathophysiological features of this subgroup are poorly defined. However, transvaginal ultrasound prior to HSG / laparoscopy identifies 34% of the patients with a hydrosalpinx. This means that many hydrosalpinges that are present may be missed if one relies on ultrasound alone.<sup>[11]</sup> It is also believed that those patients with ultrasonographically visible hydrosalpinx have a poorer outcome if it is not removed. These also tend to enlarge more during ovarian stimulation. The mechanism of the enlargement of hydrosalpinges during ovarian stimulation is unknown.<sup>[12]</sup> In experimental conditions, distal occlusion results in a very slow distension of the mechanically induced hydrosalpinx, taking more than 12 weeks, whereas, the combination of a distal and proximal block results in a significant distension within two weeks. It can be speculated that uterine junctional zone contractions play a fundamental role in the movements of both uterine and tubal fluids.<sup>[13,14]</sup> The altered fluid movements caused by the junctional zone contractions during ovarian stimulation, in the presence of a thin-walled hydrosalpinx, could be responsible for the adverse effect, for example, by acting as a mechanical barrier to embryo implantation.<sup>[12,14-16]</sup>

### IS THERE A ROLE FOR SALPINGOSCOPY IN SELECTING CASES FOR TUBAL SURGERY?

The question to address is, how the patients that are most suitable for functional surgery can be selected?

The studies of Dechaud *et al.*<sup>[17]</sup> Strandell *et al.*<sup>[18]</sup> indicated the removal of thick-walled hydrosalpinges as well as the ones that are sonographically visible. Also, it is to be remembered that the sonographically visible hydrosalpinx is always likely to be a thin-walled hydrosalpinx. Thick-walled hydrosalpinges with a mean diameter of one to two centimeters, a wall thickness of 2–10 mm, and a frequently obliterated lumen are not likely to distend during ovarian stimulation and are, or become, visible on an ultrasound.<sup>[19,20]</sup>

Vasquez *et al.*<sup>[21,22]</sup> in a prospective study, concluded that mucosal adhesions were the most important factors in

determining the fertility outcome. Their study with thin-walled hydrosalpinges showed that in the presence of normal or flattened mucosa, with no mucosal adhesions, there was a 58% pregnancy rate and a low risk of tubal pregnancy. However, thin-walled hydrosalpinges with mucosal adhesions had a high rate of tubal pregnancy, and thick-walled hydrosalpinges with fibrosis of the wall were incompatible for a normal pregnancy.<sup>[20-22]</sup>

However, tubal endoscopy has not yet gained widespread clinical acceptance.<sup>[23]</sup> Several studies on hydrosalpinges have shown that when salpingoscopy can exclude the presence of mucosal adhesions it can thereby identify the subgroup with a more than 50% intra-uterine and a less than 5% tubal pregnancy rate following reconstructive surgery.<sup>[24-29]</sup> Functional surgery is, therefore, indicated in patients with thin-walled hydrosalpinges with minimal or no mucosal adhesions. It is, however, unclear whether these patients represent the same subgroup as the patients with sonographically visible hydrosalpinx.

### HYDROSALPINX FLUID

Many retrospective studies have shown that the hydrosalpinx is associated with poor IVF outcome.<sup>[3,4,15,30-32]</sup> Recent data suggest that women with hydrosalpinx constitute a heterogeneous population with potentially different outcomes.<sup>[20,32,33]</sup> It would be valuable to identify a subset of patients who would benefit most from elective salpingectomy. The area of major concern is whether or not there is an impact on ovarian function. Many studies have reported that there is no effect on ovarian response,<sup>[3,4,20,34]</sup> some mention equivocal response,<sup>[32,33,35,36]</sup> and some show that there is a definite decrease in ovarian response the blood supply is affected during salpingectomy.<sup>[37]</sup> The role of hydrosalpinx aspiration at oocyte retrieval still awaits evaluation in a well-designed prospective trial.<sup>[38-40]</sup>

### CONSTITUENTS OF HYDROSALPINX FLUID<sup>[15]</sup>

Epidermal growth factor (EGF)  
Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )  
Cytokines  
Integrin  $\beta$   
Growth factors

### WHY IS THERE REDUCED FERTILITY WITH HYDROSALPINX?

The answer to this will be evident only when we understand the possible mechanisms causing embryotoxicity. To date, there are no reasons that are clearly defined. However,

there have been a variety of cause-effect postulations by different authors. The hydrosalpinx fluid is suggested to act on two different target systems: directly on the transferred embryos or on the endometrium and its receptivity for implantation, or both. There are many theories postulated, but none actually proven. We mention them all in brief here as it is not possible to discuss all of them at length.<sup>[3,4,6,7,9,13-15,31-33]</sup>

In spite of so much research and so many theories, there is no single explanation over a period of decades. The evidence clearly points to adverse effects in the presence of a hydrosalpinx and these are due to:

- a) Mechanical effects
- b) Embryo and gametotoxicity
- c) Alterations in endometrial receptivity markers, resulting in poor implantation
- d) Direct effect on the endometrium, leading to intrauterine fluid formation

### QUESTIONS REGARDING THE MECHANISM OF TOXICITY OF THE HYDROSALPINX FLUID THAT ARE STILL UNANSWERED

1. *Are there any embryotoxic properties of the hydrosalpinx fluid* — the doubt raised is — is there a common toxin or are there individual variations?
2. *Is the hydrosalpinx fluid toxic* — there are no pathogenic microorganisms, but there are elevated concentrations of endotoxins in the fluids.
3. *Oxidative stress?* Oxidative stress has been defined as an elevation in the steady-state concentration of various reactive oxygen species on a cellular level, and has been suggested to be of importance in hydrosalpinx cases.<sup>[41]</sup> This hypothesis needs further evaluation.
4. *Do transferred embryos starve in the presence of hydrosalpinx fluid?* Glucose rather than pyruvate is the energy substrate needed during the development of blastocysts. Studies on embryo development in the hydrosalpinx fluid suggest a lack of nutrients, which explains the impaired development of blastocysts. Is this the possible explanation for the reduced implantation rates?<sup>[31,32,42-44]</sup>
5. *Does it affect endometrial receptivity?* There is evidence to suggest that the link to implantation is the cross-talk between the embryo and endometrium. The dialogue between the embryo and endometrium is mediated by the secretion and expression of certain cytokines and other substances during the implantation window. This balance may be disturbed in the presence of hydrosalpinx fluid.<sup>[1,31,45-47]</sup>
6. *Are embryos simply washed out?* The leakage of hydrosalpingeal fluid through the uterine cavity,

resulting in the disposal of embryos, has been suggested as a mechanism by several authors.<sup>[13-15,30,31,48]</sup>

7. *Does hydrosalpinx fluid cause increased endometrial peristalsis?* Ijland *et al.*, investigated the relationship between endometrial wave-like activity and fecundability, in spontaneous cycles. Conception cycles showed the slowest wave production. There may also be a role of reflux of the fluid from the tube due to a pressure gradient.<sup>[16,20,30,32]</sup>

## CONCLUSIONS

Hydrosalpinx is a common cause of female infertility. Lower implantation and pregnancy rates have been reported in women with hydrosalpinges. How hydrosalpinx exerts its negative effect on the implantation process is not clearly understood. It is intriguing that there is an effective treatment (salpingectomy) for its management, but we do not know how and why it works. It is not only of academic interest to know this, it is also of clinical value. In women who are identified to have hydrosalpinges during controlled ovarian stimulation, during IVF, aspiration of hydrosalpinges during oocyte collection may be effective in improving pregnancy rates. Laparoscopic surgery has a place in the diagnosis and management of the hydrosalpinx. Further randomized trials are required to assess other surgical treatment options for the hydrosalpinx, such as, laparoscopic salpingostomy, laparoscopic or hysteroscopic tubal occlusion, and drainage of the hydrosalpinx before or during oocyte retrieval.<sup>[40,50]</sup>

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