Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Endometrial TNF-α, Caspase-9, Hsp70, and LIF Expression in Hydrosalpinx: Implications for Implantation Failure

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Article Info

10.24200/jogcr.10.11.860

Received: 2025/05/26
Accepted: 2025/07/12
Published Online: 01 Oct. 2025

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ABSTRACT

Background & Objective: Hydrosalpinx has been associated with impaired endometrial receptivity and reduced fertility. This study was conducted with aim to examine the expression of Tumour Necrosis Factor-alpha (TNF-α), caspase-9, Heat shock protein 70 (Hsp70), and Leukaemia Inhibitory Factor (LIF) in the endometrium of women with and without hydrosalpinx.

Materials & Methods: This cross-sectional study was conducted between May and June 2017 across three referral hospitals. A total of 48 reproductive-aged women undergoing endometrial biopsy were enrolled and equally divided into two groups: those diagnosed with hydrosalpinx and healthy controls. Immunohistochemical staining was used to assess the expression of TNF-α, caspase-9, Hsp70, and LIF. Semi-quantitative analysis was performed using histoscore evaluation of staining intensity and distribution.

Results: The hydrosalpinx group compared to the control group significantly exhibited higher expression of TNF-α (median 12 vs. 9) and caspase-9 (12 vs. 8.5), and lower expression of Hsp70 (6 vs. 8) and LIF (9 vs. 12) ($P<0.001$ for TNF-α, caspase-9, and Hsp70; $P<0.05$ for LIF, respectively).

Conclusion: Hydrosalpinx is associated with altered expression of inflammatory and apoptotic markers in the endometrium, including elevated TNF-α and caspase-9 and reduced Hsp70 and LIF. These molecular disruptions may impair endometrial receptivity and contribute to infertility, highlighting potential targets for therapeutic intervention.

Keywords: Fallopian tube disease, Tumor necrosis-alpha, Caspase 9, HSP70 heat-shock proteins, Leukemia inhibitory factor

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1. Introduction

Infertility affects approximately15% of couples of reproductive age globally (1). Tubal pathology contributes to 25-35% of infertility cases among women (2). Hydrosalpinx, defined by abnormal fluid accumulation within the fallopian tube, represents a significant tubal pathology associated with implantation failure (3,4). The composition of hydrosalpinx fluid remains uncharacterized; however, Tumor Necrosis Factor-alpha (TNF-α) is consistently detected. TNF-α regulates cellular proliferation and differentiation through multiple pathways, notably by promoting the cleavage procaspase-9 into its active form, caspase-9, a key mediator of apoptosis (5,6). Additionally, endometrial cells regulate apoptotic processes by producing chaperone proteins such as Heat shock protein 70 (Hsp70), a cytoprotective molecule known to inhibit apoptosis (7). Optimal endometrial receptivity is essential for successful embryo implantation. This process is mediated by a range of bioactive molecules, including Leukemia Inhibitory Factor (LIF), Interleukin-1 (IL-1), Interleukin-6 (IL-6), prostaglandins, and cell adhesion Molecules (CAMs). Among these, endometrial secretion of LIF and IL-6 plays a key role in modulating the endometrial environment to support blastocyst implantation (8). In conditions such as hydrosalpinx, a reduction in endometrial receptivity is low, leading to impaired implantation and subsequent infertility (9). The present study was conducted with aim to investigate the etiopathological roles of TNF-α,

caspase-9, and Hsp70 in the impairment of endometrial receptivity among women with hydrosalpinx.

2. Materials and Methods

This cross-sectional observational analytic study involved two groups: women diagnosed with hydrosalpinx and those without. The target population comprised patients who had undergone diagnostic laparoscopy at Dr. Hasan Sadikin Hospital, Graha Bunda Hospital, and Limijati Maternity and Children Hospital. Participants were recruited using consecutive sampling from May to June 2017.

The inclusion criteria were as follows: For the case group: women aged 21-42 years with confirmed hydrosalpinx and no other gynecological abnormalities, regular menstrual cycles (21-35 days), and married; For the control group: women aged 21-42 years without hydrosalpinx on laparoscopy, regular menstrual cycles (21-35 days), including those with idiopathic infertility undergoing diagnostic laparoscopy and those undergoing laparoscopic sterilization. The exclusion criteria were: history or clinical evidence of malignancy, endometriosis, or autoimmune disorders; use of immunomodulatory drugs within the past 3 months; current pregnancy; hormonal treatment with GnRH agonists, estrogen, or progesterone within the past 6 months; and use of an intrauterine device within 6 months before the study.

The sample size was determined as 24 participants for each group, yielding a total of 48 subjects for the study. Following recruitment, all participants underwent diagnostic laparoscopy. Based on intraoperative findings, they were assigned to either the hydrosalpinx or control group. Subsequently, endometrial biopsies were obtained from all subjects. The collected samples were analyzed using Immunohistochemistry (IHC) with antibodies targeting TNF-α, caspase-9, Hsp70, and LIF. Staining was conducted using the streptavidin-biotin technique **(10)**.

Immunohistochemistry of Samples and Analysis

Paraffin-embedded endometrial tissue blocks were sectioned at a thickness of 4 μm and initially treated with 0.3% hydrogen peroxide in methanol for 15 minutes at room temperature to inhibit endogenous peroxidase activity. After rinsing with phosphate-buffered saline (PBS; pH 7.4), nonspecific binding was blocked by incubating the sections with 10% normal serum for 30 minutes. The slides were then incubated for 60 minutes with the following primary monoclonal antibodies: anti-TNF-α (mouse monoclonal, 2C8), caspase-9 (rabbit monoclonal, E23), Hsp70 (rabbit monoclonal, EPR16892), and LIF (rat monoclonal, IMG39N7D10), all from Abcam. Then, a secondary antibody (Starr Trek HRP Universal Detection System) was applied and incubated for 15 minutes at room temperature. Immunoreactivity was visualized using diaminobenzidine tetrahydrochloride (DAB) as the chromogen, and counterstaining was performed with Mayer's hematoxylin.

Staining intensity was semi-quantitatively evaluated based on two parameters: intensity (graded 1+ to 3+, with 3+ indicating strong staining) and the percentage of positive cells (<20%=1, 20-50%=2, 50-80%=3, >80%=4). Statistical analysis was conducted using SPSS software (version 16.0) **(11)**. Mann-Whitney U test and regression analysis were applied where appropriate. $P<0.05$ was considered statistically significant.

3. Results

The study recruited 48 subjects, equally divided into two groups. The demographic characteristics of the participants revealed no significant differences in age distribution ($P=0.311$) or BMI ($P=0.807$). The age and BMI were similarly distributed across both groups, ensuring that the comparative analysis of other variables, such as protein expression related to endometrial receptivity, would not be confounded by these factors (Table 1).

TNF-α expression was significantly higher in the hydrosalpinx group compared to the non-hydrosalpinx group, based on staining intensity, cellular distribution, and histoscore analysis ($P<0.05$) (Figure 1) (Table 2).

Moreover, caspase-9 levels were markedly increased in the endometrium of patients with hydrosalpinx relative to controls ($P<0.05$) (Figure 2) (Table 3).

There was a substantial reduction in Hsp70 expression in the hydrosalpinx group compared to the non-hydrosalpinx group ($P<0.05$) (Figure 3) (Table 4).

LIF expression was significantly lower in the hydrosalpinx group compared to controls, as indicated in Figure 4 and Table 5 ($P<0.05$).

Table 6 presents the correlation analysis of TNF-α, caspase-9, and Hsp70 with LIF expression, highlighting their roles in endometrial receptivity. The regression model-Histoscore LIF=4.198+(0.396×Hsp70 histoscore)+(0.365×Caspase-9 histoscore)-(2.805×Group)- suggests that Hsp70 and caspase-9 positively influence LIF expression, while TNF-α didn't show a significant effect.

Table 1. Characteristics of Study Subjects

Characteristics	Group		P-value*
	Hydrosalpinx (n=24)	Non-hydrosalpinx (n=24)	
Age (Years old)			0.311
<30	8	4	
30-35	10	10	
>35	6	10	
Body Mass Index			0.807
Normal	12	10	
Overweight	10	11	
Obese	2	3	

*chi-squared test

Table 2. TNF-α Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx

TNF-α	Group		P-value*
	Hydrosalpinx (n=24)	Non-hydrosalpinx (n=24)	
Intensity			
Low	0	5	
Moderate	21	12	
Strong	3	7	
Distribution			
20-50	0	1	
50-80	0	20	
>80	24	3	
Histoscore			<0.001
Median	12	9	
Range	12-16	6-12	

*Mann-Whitney U test

Table 3. Caspase-9 Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx

Caspase - 9	Group		P-value*
	Hydrosalpinx (n=24)	Non-hydrosalpinx (n=24)	
Intensity			
Low	1	11	
Moderate	16	11	
Strong	7	2	
Distribution			
20-50	0	1	
50-80	3	8	
>80	21	15	
Histoscore			<0.001
Median	12	8.5	
Range	8-16	6-16	

*Mann-Whitney U test

Table 4. Hsp70 Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx

Hsp70	Group		P-value*
	Hydrosalpinx (n=24)	Non-hydrosalpinx (n=24)	
Intensity			
Low	17	15	
Moderate	4	3	
Strong	3	6	
Distribution			
20-50	0	1	
50-80	24	2	
>80	0	21	
Histoscore			<0.001
Median	6	8	
Range	6-12	6-16	

*Mann-Whitney U test

Table 5. LIF Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx

LIF	Group		P-value*
	Hydrosalpinx (n=24)	Non-hydrosalpinx (n=24)	
Intensity			
Low	9	5	
Moderate	7	11	
Strong	8	8	
Distribution			
20-50	0	3	
50-80	24	0	
>80	0	21	
Histoscore			0.008
Median	9	12	
Range	6-12	6-16	

*Mann-Whitney U test

Table 6. Correlation TNF-α, Caspase-9 dan Hsp70 with LIF Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx

Variables	Coefisien B	Std. Error	Beta	t	P-value
Constanta	4.198	2.064		2.034	0.048
Caspase-9	0.365	0.144	0.356	2.529	0.015
Hsp70	0.396	0.133	0.395	2.975	0.005
Groups	-2.805	0.940	-0.443	-2.983	0.005

histoscore TNF-α; P=0,148. Groups score (0=non-hydrosalpinx, 1=hydrosalpinx)

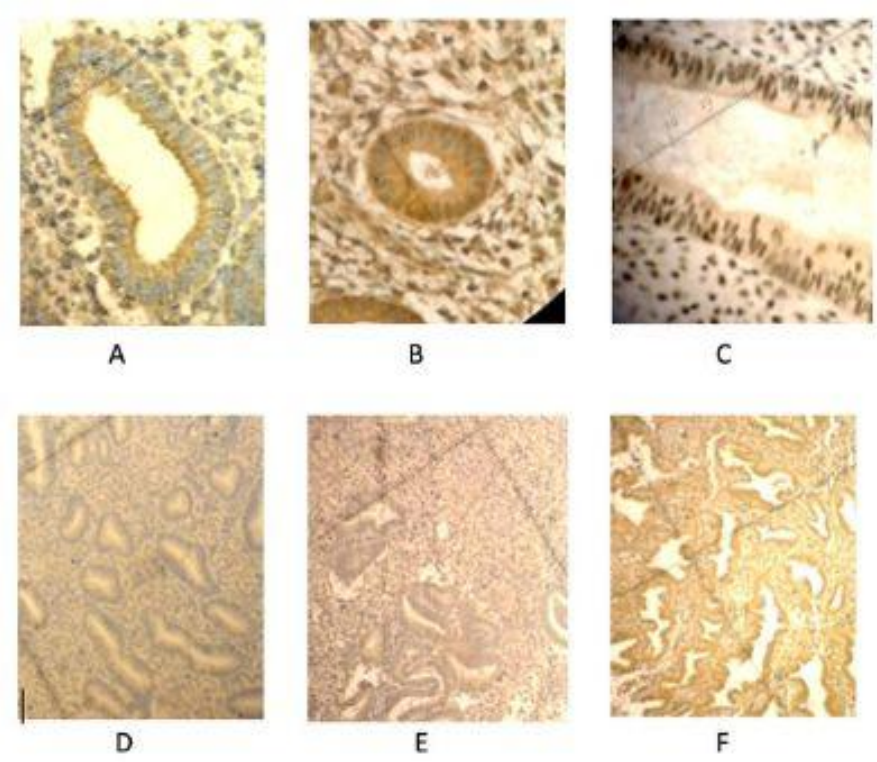


Figure 1. TNF-α Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx. A) TNF-α endometrium expression with low intensity (400x). B) TNF-α endometrium expression with moderate intensity (400x) C) TNF-α endometrium expression with strong intensity (400x). D) TNF-α endometrium expression with 20–50% distribution (100x). E) TNF-α endometrium expression with 50–80% distribution (100x). F) TNF-α endometrium expression with >80% distribution (100x).

Figure 2. Caspase-9 Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx. A) Caspase-9 endometrium expression with low intensity (400x). B) Caspase-9 endometrium expression with moderate intensity (400x). C) Caspase-9 endometrium expression with strong intensity (400x). D) Caspase-9 endometrium expression with 20–50% distribution (100x). E) Caspase-9 endometrium expression with 50–80% distribution (100x). F) Caspase-9 endometrium expression with >80% distribution (100x).

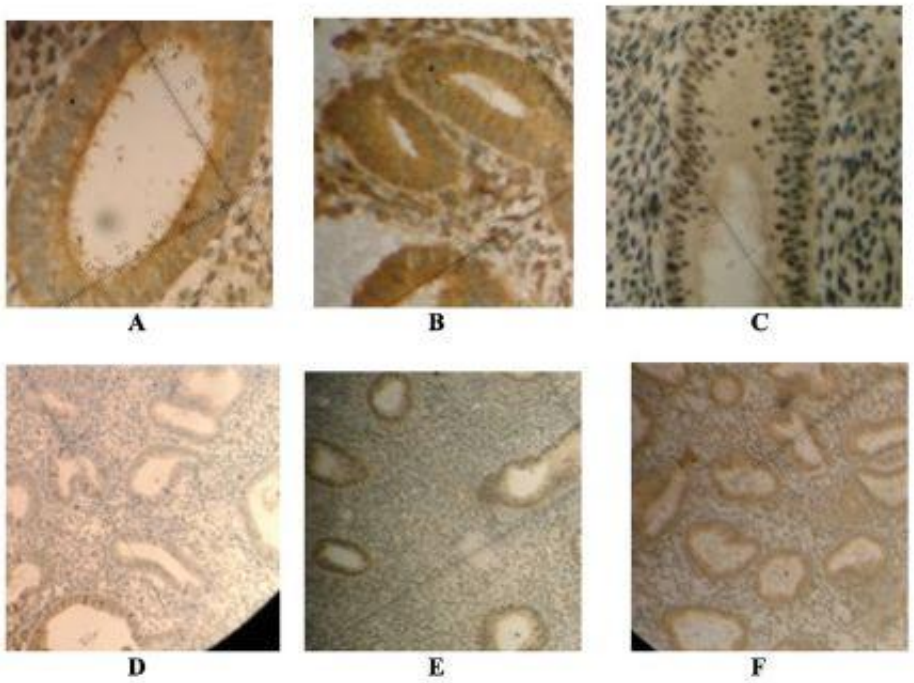


Figure 3. Hsp70 Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx. A) Hsp70 endometrium expression with low intensity (400x). B) Hsp70 endometrium expression with moderate intensity (400x). C) Hsp70 endometrium expression with strong intensity (400x). D) Hsp70 endometrium expression with 20–50% distribution (100x). E) Hsp70 endometrium expression with 50–80% distribution (100x). F) Hsp70 endometrium expression with >80% distribution (1

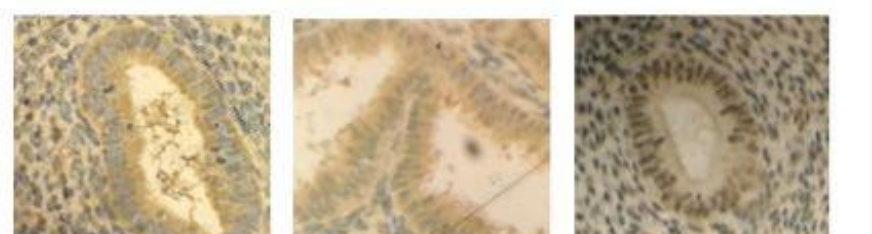


Figure 4. LIF Endometrium Expression between Hydrosalpinx and Non-hydrosalpinx. A) LIF endometrium expression with low intensity (400x). B) LIF endometrium expression with moderate intensity (400x). C) LIF endometrium expression with strong intensity (400x). D) LIF endometrium expression with 20–50% distribution (100x). E) LIF endometrium expression with 50–80% distribution (100x). F) LIF endometrium expression with >80% distribution (100x).

4. Discussion

In response to intracellular pathogens, inflammatory processes are accompanied by elevated levels of cytokines such as TNF-α, predominantly produced by activated macrophages. TNF-α is pivotal in regulating cellular proliferation, differentiation, and immune modulation, serving key functions in controlling inflammation, immune defense, and programmed cell death **(12)**. Additionally, TNF-α functions as a crucial defense mediator against the proliferation of tumor cells, microorganisms, and parasitic pathogens. In the context of hydrosalpinx, the inflammatory response observed in the endometrium is partly attributed to the distinct composition of hydrosalpinx fluid, which differs significantly from normal tubal fluid in its capacity to infiltrate the endometrial tissue and activate resident macrophages **(13,14)**. When hydrosalpingeal fluid enters the endometrial cavity, it can stimulate the activation of macrophages and epithelial cells, resulting in elevated TNF-α expression **(15)**. The present study identified TNF-α expression in the non-hydrosalpinx group, consistent with its physiological presence in endometrial tissue and myometrial smooth muscle cells under normal conditions.

Previous studies have shown the involvement of TNF-α in regulating endometrial apoptosis and suggested that excessive TNF-α production in the spiral arteries may contribute to the physiological processes of menstruation **(16)**. Apoptosis of endometrial cells is a crucial regulatory mechanism that maintains endometrial function during the menstrual cycle and embryo implantation. The implantation process naturally requires a controlled apoptotic response. Dysregulation of apoptosis within the endometrium may compromise endometrial receptivity, thereby contributing to implantation failure **(17)**.

In the present study, caspase-9 expression was markedly elevated in the endometrium of patients with hydrosalpinx compared to those without, suggesting that the pathophysiology of hydrosalpinx may involve molecular dysregulation, including altered caspase-9 expression, which disrupts endometrial homeostasis and promotes apoptosis. This finding aligns with research by Madjid et al., who reported increased caspase-9 expression in the endometrial cells of endometriosis patients **(18)**. This finding suggests that endometriosis affects the microenvironment of the peritoneal fluid and uterine cavity, inducing elevated caspase-9 activation within the endometrium. Neither the physiological nor pathological conditions discussed herein necessitate the presence of anti-apoptotic factors. Notably, Hsp70 has been demonstrated to indirectly inhibit apoptotic pathways involving caspases **(19)**.

In the present study, Hsp70 expression was lower in the hydrosalpinx group. This inverse correlation between Hsp70 and caspase-9 supports a model where diminished cytoprotection contributes to heightened apoptotic activity **(19,20)**. TNF-α and caspase-9 are closely associated with the induction of apoptotic activity, whereas Hsp70 exhibits anti-apoptotic functions. This indicates an inverse functional relationship between Hsp70 and both TNF-α and caspase-9, where higher levels of Hsp70 are typically

associated with suppressed apoptotic pathways initiated by TNF-α and executed by caspases **(20)**.

LIF is a crucial cytokine that acts as a significant marker for endometrial receptivity, playing an essential role in establishing optimal conditions for embryo implantation **(21)**. LIF exhibits elevated expression within the endometrium, commencing in the mid-secretory phase and persisting through the late secretory phase (approximately Days 18-28 of the menstrual cycle). A peak in LIF expression is typically observed around Day 20 of the menstrual cycle and continues into early pregnancy **(22)**. In the present study, LIF levels were lower in the hydrosalpinx group compared to the non-hydrosalpinx group, indirectly indicating that the presence of hydrosalpinx negatively affects endometrial receptivity. The reduced receptivity marked in the hydrosalpinx group is likely attributable to the influx of hydrosalpinx fluid into the uterine cavity, which disrupts the uterine environment and impairs cytokine communication crucial for embryo implantation **(23)**.

Prior research has demonstrated that LIF expression in hydrosalpinx patients significantly changes following surgery. Specifically, LIF levels in these patients were lower before the procedure **(8)**. This outcome suggests that the proapoptotic mediators associated with hydrosalpinx, as previously described, exert a suppressive effect on LIF, thereby indirectly representing the state of the implantation window in this condition. The association of TNF-α, caspase-9, and Hsp70 with LIF and endometrial receptivity explains the underlying pathophysiology of hydrosalpinx. Existing literature consistently reports the detrimental effects of fluid generated within the hydrosalpinx, with several studies demonstrating its toxic impact on fertility **(24)**.

The present study investigates how hydrosalpinx impairs endometrial receptivity by activating apoptosis-related signaling pathways. When hydrosalpinx fluid enters the uterine cavity, it stimulates macrophages, increasing local TNF-α concentrations. There was a significantly higher TNF-α expression in the endometrial tissue of women with hydrosalpinx compared to controls in the present study. This excess TNF-α is set to provoke the extrinsic apoptotic cascade, where ligand molecules in this case, TNF-α produced by neighboring cells bind to death receptors on target cells rather than being synthesized by the targets themselves **(15)**. Specifically, TNF-α engages Tumor Necrosis Factor Receptor-1 (TNFR1) in endometrial epithelial cells, subsequently recruiting the adaptor protein TNFR1-Associated Death Domain (TRADD). TRADD, in turn, is associated with the Fas-Associated Death Domain (FADD), ultimately leading to caspase-8 activation. Given that LIF is a critical marker of endometrial receptivity—endogenously produced within endometrial epithelial cells, any influence of TNF-α on LIF expression must be indirect and mediated through this described apoptotic signaling cascade **(25,26)**. The limitation of our study was that we quantified TNF-α expression but did not assess downstream TRADD levels in endometrial tissue, preventing direct confirmation of the proposed mechanism.

Notably, caspase-9, a key mediator of the intrinsic apoptotic pathway, exhibited elevated expression in patients with hydrosalpinx. Conversely, Hsp70, known for its cytoprotective and anti-apoptotic properties, showed diminished expression in the hydrosalpinx cohort. This inverse relationship between caspase-9 and Hsp70 in the present study suggests a heightened apoptotic process in these patients, consistent with the significant role of Hsp70 in suppressing mitochondrial-intrinsic apoptotic pathways. Furthermore, elevated apoptosis can directly suppress Hsp70 expression within endometrial cells **(27)**. Unlike TNF-α, which originates extracellularly, both caspase-9 and Hsp70 are generated intracellularly within endometrial cells, as is LIF. Our findings indicate that the dysregulation of both caspase-9 and Hsp70 significantly contributes to the altered LIF levels observed in hydrosalpinx.

This study had some limitations. It concentrated solely on four specific proteins within the apoptotic pathway that are hypothesized to contribute to diminished endometrial receptivity in patients with hydrosalpinx. Given the intricate nature of apoptosis, numerous other mechanisms and proteins involved in this process warrant further investigation. Furthermore, the correlation between endometrial receptivity and protein expression was assessed indirectly via immunohistochemical techniques. Future research should aim to directly elucidate the mechanisms by which hydrosalpinx impacts endometrial receptivity to advance understanding and therapeutic strategies.

5. Conclusion

This study highlights the molecular disruption of endometrial receptivity in women with hydrosalpinx, characterised by increased expression of pro-apoptotic markers TNF-α and caspase-9, and decreased levels of the cytoprotective protein Hsp70 and implantation-supportive cytokine LIF. The correlations between caspase-9 and Hsp70 with LIF suggest that both apoptotic and protective intracellular mechanisms play a key role in regulating receptivity. These findings indicate that hydrosalpinx creates a hostile endometrial environment that may impair implantation, contributing to infertility. Understanding these molecular alterations provides a foundation for developing targeted interventions to improve reproductive outcomes in affected women.

6. Declarations

Acknowledgments

None.

Ethical Considerations

The Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran, granted ethical approval for this study under registration number 572/UN6.C10/PN/2017. All participants provided written informed consent to participate in the examination of patients adhered to the ethical standards outlined in the 1964 Declaration of Helsinki.

Authors' Contributions

Hanom Husni Syam, Jusuf Sulaeman, Effendi Ponpon Idjradinata and Tita Husnitawati Madjid contributed to the conception and design of the study, data collection, molecular assessment, provision of materials and patients, statistical analysis, and drafting the manuscript

Conflict of Interest

The authors declare no competing interests.

Fund or Financial Support

No external funding was received for this study.

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How to Cite This Article:

Husni Syam, H., Sulaeman Effendi, J., Idjradinata, P., Husnitawati Madjid, T. Endometrial TNF-α, Caspase-9, Hsp70, and LIF Expression in Hydrosalpinx: Implications for Implantation Failure. J Obstet Gynecol Cancer Res. 2025;10(11):860-8.

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