Review Article

# Human Follicular Fluid, Clinical Use of Proteomics Analysis in Identification of Infertility

**Nidhi Gairola[1,2,*], Mahamedha Deorari[1], Vikash Jakhmola[1], Reema Sircar[3], Havagiray R Chitme[2,*]**

[1]Uttaranchal institute of Pharmaceutical Sciences, Uttaranchal University Dehradun, Uttarakhand, INDIA.
[2]Faculty of Pharmacy, DIT University, Dehradun, Uttarakhand, INDIA.
[3]Senior Consultant & Head, Indira IVF, Dehradun, Uttarakhand, INDIA.

## ABSTRACT

**Introduction:** In present situation infertility is one of the chief problem for reproductive couples due to multiple factors including lifestyle. Infertility is thought to be caused by both male and female factors in 27 percent of cases, with 15 percent of cases being idiopathic. Assisted reproductive technologies are used by these couples to overcome the problems related to infertility, but the success rate of ART is appreciated by WHO if it reaches to 30%. About 70% non-successful ART is due to the fact that molecular mechanism of human reproductive system is poorly understood. **Materials and Methods:** A systematic review was carried out using which pubmed, sciencedirect, scifinder, and google scholar databases. We followed standard criterion of inclusion and exclusion recommended by Cochrane review system. Information collected from the selected articles were compared and summarized in tables and Figures. **Results:** Proteomics is a promising approach for identifying possible biomarkers for infertility treatment and management. The use of OMICS technology to develop diagnostic and therapeutic techniques to increase the efficacy of ART is critical. Tandem mass spectrometry (LC-MS/MS) is used to identify peptides in proteins. Using advance proteomics tools such as SELDI-TOF, MALDI-TOF stressing the importance of protein in pregnancy maintenance and fertilization. **Conclusion:** We conclude from this study that using proteomics analysis can help in identifying potential biomarkers which can be used in the field of diagnostic and therapeutic of infertility. Further serious and extensive research is very much required in this field of research.

**Keywords:** Infertility, Assisted reproductive technologies, Proteomics, Therapeutic Management.

## INTRODUCTION

Currently, infertility is common problem for reproductive age group females. With recent publication 27% of infertility is caused due to both male and female factors. It is estimated that about 38% of factors are related to female, 20% are of male and remaining are idiopathic.

There are multiple factors which are contributing to infertility in female like hormonal imbalances, genetic (5-10%) and environmental factors, any specific disease. Other than these there are some other less commonly known pathophysiological factors such as Polycystic Ovary Syndrome (PCOS) and endometriosis.[1]

Infertility due to PCOS has been associated with increased insulin resistance, hyperlipidemia, type II diabetes, hyper adiposity. Endometriosis has been linked with asthma, cardiovascular disorder, autoimmune disorder, atopic disease and ovarian cancer.

Diagnosis of infertility in female is subjective because it is very critical to understand basic mechanism coupled with the etiology of this condition. In the study of human reproduction, proteomics is widely used. The application of technology for the identification and quantification of proteins present on a specific cell or organism was part of a proteomics

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**Correspondence:**
***Dr. Havagiray R. Chitme***
Faculty of Pharmacy
DIT University, Dehradun,
Uttarakhand - 248009,
INDIA.
E-mail: hrchitme@gmail.com

www.ijper.org

investigation. Proteomics based study has been used to identify the molecular mechanism associated to normal gametogensis and function of protein in fertilization.

Proteomics has proven to be an effective approach for identifying infertility biomarkers. Bioinformatics and proteomic data analysis provide functional knowledge on the proteins that regulate biological processes relevant to reproductive function. It has the potential to be employed as a biomarker in the diagnosis and treatment of infertility.

## FOLLICULAR FLUID

Follicular fluid is a biological fluid composed of antioxidants, hormones, steroids, reactive oxygen species, electrolytes, enzymes anticoagulants that surrounds the developing oocyte and carrying nutrient to oocyte. The primary function of follicular fluid is to protect follicular cells from oxidative and physical damage while also allowing them to communicate with one another.[2]

Theca cells, as well as the oocyte and granulose cells within follicles, release folicular fluid as demonstrated in Figure 1. It is filterd through basal membrane which act as a molecular filter. Molecule which have high molecular weight can cross the basal membrane and enter in to FF. This is why FF has low levels of fibrinogen, a high molecular weight protein that does not coagulate.

Follicular fluid comprises a number of proteins that are important for follicular development and oocyte maturation during folliculogenesis. Follicular fluid contain more than 742 proteins which effect the development of oocyte and follicular maturation.[3] Problem related to infertility can solve by protein (Proteomics) analysis and assisted reproduction technology.[4]

Proteomics analysis is a noninvasive technique for learning about follicular and oocyte development. For the treatment of infertility and ovarian stimulation, the identification of specific indicators such as normal and premature luteinization can help to improve the outcome of ovarian stimulation. A comprehensive study about proteomics analysis provide a good data base of follicular fluid protein and that should be useful for study of physiology and pathology of ovary and other infertility disorder. Several methods for identifying distinct proteomics in various groups of follicular fluid during folliculogenesis in fertile and infertile women during invitro fertilization have been documented.[5-6]

Current aim of proteomics analysis is to identify role of these protein in infertility disorder like (PCOS, endometriosis, ovarian cancer etc) and identify physiology of ovarian and reproductive system.[7-8]

There are around 617 unclear proteins have been discovered, according to Bianchi *et al*. Using the DAVID analysis programme, 337 proteins were found to have various functional categories.[9] Mostly groups represent 28% inflammation and 22% wound response of FF protein. This justifies that ovulation is a short-term inflammatory process that is followed by tissue healing.[10]

Changes in the molecular contents of follicular fluid proteomics are associated with advanced ageing and specific medical diseases such as ovarian dysfunction PCOS, OHSS, infertility, and miscarriage.

Poor ovarian response or any other infertility disorder can predicted potential biomarker by Quantitative proteomics analysis. In one comparative study of Indira pla *et al*.[11] By hsAF 2461 proteins were identified from FF where 1108 were new proteins. In Oh *et al*. Identified 1108 proteins follicular protein in assisted reproductive treatment (ART) of infertile female when compared with normal female. It will be beneficial for infertility disorders and identification of biomarker screening in patients.[12]

**Proteomics Analysis:** proteomics analysis means study of complete profile of protein present in sample. Using proteomics tools and techniques we can understand physiology, molecular mechanism of reproductive system and also provide diagnosis, therapeutic management to infertility related disorders.[13-14] On the basis of protein and condition proteomics can be classified as expression proteomics, structural proteomics, and functional proteomics.[15]

As demonstrated in Figure 2 both bioinformatics and analytical tools are employed for proteomics analysis. 2-D gel electrophoresis and mass spectrometry – MALDI-TOF-MS are the most prevalent techniques used in proteomics. Isotope-coded affinity tags (ICAT), Isobaric Tags for Relative and Absolute Quantification (iTRAQ), Absolute Quantification (AQUA), ESI-

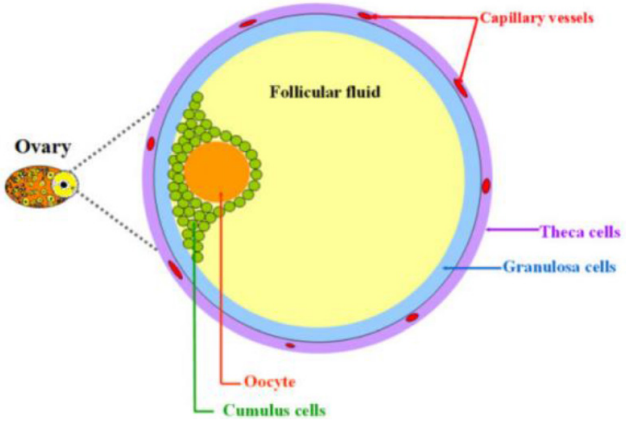


**Figure 1: Follicular Fluid.[13]**

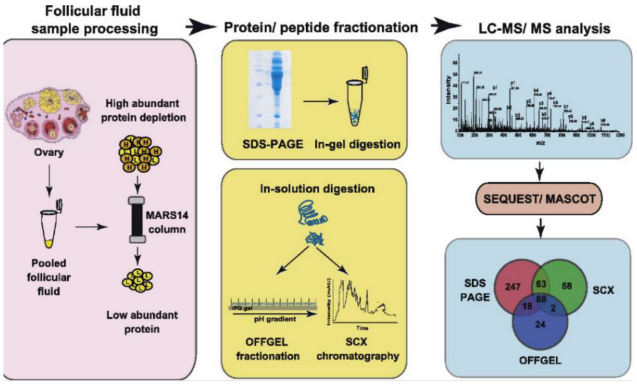


**Figure 2: Follicular Fluid Sample Processing.**[17]

Q-IT-MS, and SELDI-TOF-MS are some other as summarized in Table.[16]

**Proteomics' Role in Female Infertility:** Follicular fluid is high in protein and peptide, and it serves as a source of sustenance for oocytes. These proteins are essential for fertilisation. Antioxidant protein, superoxidation, and the acute phase of proteins HSP27 are all found in follicular fluid. Follicular proteins include metalloproteinase, thrombin, and vitamin-D receptor, transferrin, complement component C3, haptoglobin, and alpha-1-antitrypsin. In IVF patients, 11 biomarkers have been discovered, with some indicating a positive and others indicating a negative response.[18]

Cumulus cells are also important in fertilization because they cover the oocyte and help it mature. Cumulus cells from pregnant and non-pregnant women were found to contain a total of 72 proteins.

In case of female reproductive system there are many disorders which can cause infertility in females like PCOS, Endometrosis and Cancer.

**PCOS:** PCOS (Polycystic Ovary Syndrome) is the most common reproductive and metabolic condition in women. Menstrual disorder and elevated androgens are linked, and this has a significant influence on their quality of life. Patients with PCOS are also more likely to develop cardiovascular disease, insulin resistance, type 2 diabetes, obesity, infertility, and a variety of other physiological problems. The pathophysiology and molecular mechanisms of PCOS remain unknown. Proteomics analysis of a PCOS patient sample can reveal molecular mechanisms and aid in the identification of molecular markers and risk factors linked with PCOS.[19] Ambekar et colleagues discovered 186 proteins in PCOS-affected women.

Overproduction of alpha-1-antitrypsin, which prevents egg maturation, is another cause of infertility.[20] Transferrin, fibrinogen, and chain variations, kininogen-1, annexin 2, and peroxiredoxin 2 proteins,

**Table of Sample and Different Method Use for Analysis of Protein.**

| Sample | Method | DEP ( differentially expressed proteins) |
|---|---|---|
| - | Review | Transgelin, pyruvate kinase M1/M2, gelsolin-like capping protein (macrophage capping protein), glutathione S-transferase P, leucine aminopeptidase (cytosol aminopeptidase), peptidyl-prolyl cis-transisomerase, cyclophilin A, complement component C4A, and manganese-superoxide dismutase are some of the proteins.[34] |
| Plasma | MALDI-TOF and 2D-DIGE | In kappa-free light chain, haptoglobin, alpha-2-macroglobulin, and transferrin.[7] |
| Follicular fluid | LC/MS-MS | plasminogen; amphiregulin; heparan sulphate proteoglycan; tumour necrosis factor, a-induced protein and lymphatic vessel endothelial cells.[10] |

according to Galazis *et al.* have been discovered as potential biomarkers in PCOS patients.[21-23]

**Endometriosis:** Endometriosis is a reproductive illness with an unknown etiology marked by the presence of endometrial tissue outside the uterine cavity, which causes infertility and chronic pain is an estrogen-dependent chronic disease.[24] Certain proteins, such as Glutamate NMDA Receptor zeta 1 and FRAT1, are changed in endometriosis. ACO2, CDC5L, GNAS, ARF1, ANPEP, SERPIND1, and SEC23B were proteins discovered in endometriosis and expressed in a GnRH antagonist-based ovarian stimulation regimen.[25] Immunity-related proteins (annexin A4 and annexin A5) and oxidative-related proteins (peroxiredoxin 2 isoform "a" and peroxiredoxin 3) were reduced regulated in endometriosis, however 14-3-3 protein associated in cell proliferation was up regulated.[26]

## Ovarian Cancer

Ovarian cancer is any cancerous growth that begins in the ovary. Exact causes of ovarian cancer are not known but certain drugs which produce ovulation, over use of that type of drug can produce risk of ovarian cancer.[28] Calreticulin, fibrinogen-c, superoxide dismutase, vimentin, malate dehydrogenase, and lamin B2 are proteins involved in ovarian cancer.[29]

**Role of Proteins and Molecular Pathways in Fertilization:** Homeostasis, cellular pathways and alteration in proteins produce regulation of fertilization. Disturbance in molecular pathway or proteins sequence such as imbalance in ROS Concentration produce oxidative stress during follicular maturation.[30] DEP

**Table 1: Table of Sample and Different Method Use for Analysis of Protein**

| Sample | Method | DEP (differentially expressed proteins) |
|---|---|---|
| Glandular epithelium | Mass Spectroscopy | Ectonucleotide pyrophosphatase/ phosphodiesterase family member 3 includes arboxypeptidase M, tenascin C, neprilysin, and ectonucleotide pyrophosphatase/ phosphodiesterase (ENPP3).[25] |
| Uterine lavage | 2D-DIGE and MS | Alpha-2-macroglobulin and antithrombin III.[27] |

showed dysregulation in IVF research, according to studies. These DEP were shown to be linked to pathways involved in immunological response, coagulation, and acute-phase reactions.[31] Endometrial Nuclear mRNA splicing via spliceosome and the energy metabolism pathway were regulated during the prolife troy phase of the endometrial metabolic route of carbohydrate biosynthetic processes as given in Table 1.[32] Other mechanisms, such as redox regulation, cell proliferation, and apoptosis, are also affected by endometrial inflammation.[33] In the case of PCOS linked to oxidative stress, metabolic processes, and inflammation, the major route is impacted.[34]

**Biomarker and Infertility:** Amphiregulin, heparan sulphate proteoglycan 2, tumor necrosis factor, a-induced protein 6, plasminogen, and lymphatic vessel endothelial hyaluronan receptor 1, suprabasin, S100 calcium binding protein A7, and transcriptional coactivator, a1-antitrypsin, apolipoprotein A-I, and transferring factor are all potential PCOS biomarkers.[35-36] RPL19, RPL5, RPL11, and RPL23, and RPL17, ATP1B4 and FGA, and CRMP2 are ribosomal proteins that mediate endometrosis. HIF1A, Vimentin, Sorcin, Cofilin-1, Apo-A1, and Ran were among[37] unidentified proteins involved in endometrosis.

**Assisted Reproductive Technology**: Assisted reproductive technology (ART) is a fertility treatment method that uses a woman's egg and a man's sperm to cure infertility.[38]

Combining an egg and sperm in a laboratory dish is one of the most used assisted reproduction techniques presented in Figure.3. When an egg fertilizes and divides, an embryo is formed, which is then delivered to a woman's uterus, where it will ideally implant in the uterine lining and develop further. This process involves the passage of fallopian tubes and can influence the decision of females with fallopian disorders.[39]

In case of Assisted reproductive technology some time used donor egg, sperm or previously frozen embryos. There can be used gestational or surrogate carrier. In case of surrogacy woman can pregnant with sperm of male partner and in case of gestational woman become pregnant with sperm from male partner and egg from female partner.[40]

In case of IVF there are 5 step basic involved:

**Other techniques used in IVF:** There are some other techniques which are used in IVF[42]

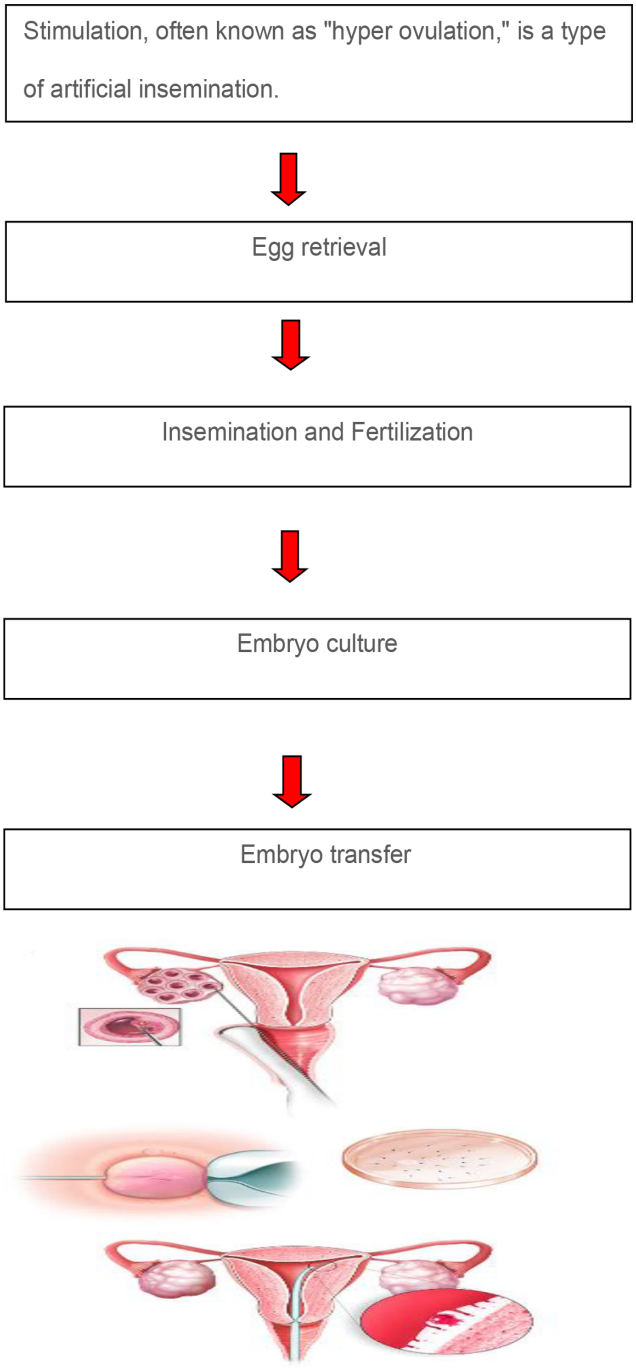


**Figure 3: Eggs are Extracted from Mature Follicles and Fertilised in a Petri Dish (Either by Inserting a Single Sperm into the Egg or by Combining the Egg with Sperm), After Which the Embryo is Placed into the Uterus.[41]**

**Gestational carrier:** Women who have a major uterine issue or a serious health risk may benefit from IVF with a gestational carrier. In this situation, the couple's embryo is implanted in the carrier's uterus in order to achieve pregnancy.

**Assisted hatching:** The embryo is implanted into the uterine lining by opening the embryo's outer shell in this approach (hatching).

**Intracytoplasmic sperm injection (ICSI):** ICSI technique is used when quality and quantity of male semen is poor or if fertilization was failed in prior attempt of IVF cycle. Healthy single sperm directly injected in to mature egg.

**Donor Eggs or Sperm**: If male or female are suffering severe problem with release or production of sperm and egg they can choose to use of egg, sperm or embryo from any other donor.

## CONCLUSION

We have gained a better understanding of human reproduction and infertility disorders because of enormous knowledge emerged through proteomics. Proteomics-identified biomarkers and proteins are extremely important in the diagnosis, treatment, and counseling of infertility-related conditions, as well as the creation of molecular techniques. OMICS technology will likely be used extensively in ART research, diagnostics, and treatments.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**PCOS:** Polycystic ovarian syndrome; **ENPP3**: ectonucleotide pyrophosphatase/phosphodiesterase; **ART:** Assisted reproductive treatment; **ICAT:** Isotope-coded affinity tags.

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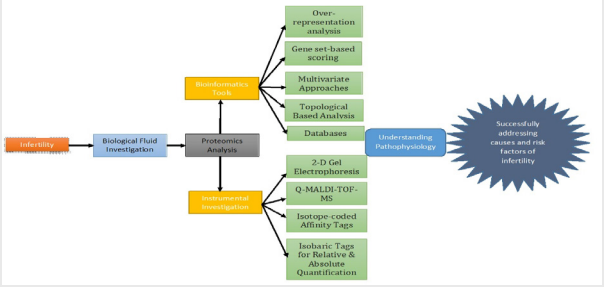
## PICTORIAL ABSTRACT




## SUMMARY

Infertility in female is one of the most complex condition in female. Understanding the cause and risk factors is important in addressing the issue. The main method of treating the infertility is through ART. However, it has limited success. Therefore there is a need to use advanced technologies and bioinformatics tools to understand the pathophysiology underlying infertility and address it. Current review article reviews the methods of infertility management and tools to be used in understanding physiology, pathology, morphology and biochemistry of infertility.

## About Authors

**Mrs. Nidhi Gairola** Currently works at Uttaranchal Institute of Pharmaceutical Sciences, Uttaranhal University, Dehradun –India as Asst. Professor and research scholar in DIT University, Dehradun, India. Her specialization is in Pharmacology.

**Havagiray R Chitme** currently works at DIT University, Dehradun- India as Professor of Pharmacology, Faculty of Pharmacy. His areas of research interest includes Clinical side of Pharmacology especially on metabolic syndrome and infertility.

**Ms. Mahamedha Deorari** Currently works at Uttaranchal Institute of Pharmaceutical Sciences, Uttaranhal University, Dehradun –India as Asst. Professor and her specialization in Pharmacognosy.

**Dr. Vikash Jakhmola** currently works at Uttaranchal Institute of Pharmaceutical Sciences, Uttaranhal University, Dehradun –India as Professor and Dean . His area of research includes Pharmaceutical Chemistry, Synthetic Chemistry, Phytochemistry.

**Dr. Reema Sircar** is a Gynecologist, Obstetrician and Infertility Specialist. She has a total experience of more than 24 years.

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