



Diagnosis and management attempts of some causes of unexplained infertility

Saeed Mohamad Ahmad Thabet^{1*}, Athmar Hussein Ali² and Fadl Mansour Al Wousabi²

*Correspondence: dr_saeedth@hotmail.com



CrossMark

← Click for updates

¹Professor of Gynecology & Obstetrics, Faculty of Medicine, Cairo University, Egypt.

²Assistant Professor of Gynecology & Obstetrics, Faculty of Medicine, Sana'a University, Yemen.

Abstract

Objective: Trying to diagnose clinically some suggested causes of unexplained infertility related to ovum picking, fertilization, embryo growth and implantation and to outline the most suitable management needed for these cases.

Design: Prospective controlled diagnostic and management study.

Setting: 50 fertile cases as control.

Patients: Assessment of ovum picking was determined clinically in 50 cases of unexplained infertility, in addition to certain causes related to fertilization, embryo growth and implantation in another 50 cases having failed IVF used for management of similar cases.

Interventions and main outcome measure: Accessibility of the ovulation site to fimbrial end of the tube and in turn ovum picking was clinically determined by the use of combined selective salpingography and ovarian sonography. Other causes were determined by determining the cause of failure of IVF used for managing similar cases of unexplained infertility.

Results: Successful clinical diagnosis of ovarian picking could be significantly obtained in 90% of the fertile cases compared to 52% of the infertile cases ($P < 0.005$). Meanwhile, failed ovum picking could be diagnosed in 42% of the infertile cases compared to only 2% of the fertile cases ($P < 0.005$). Other causes were also diagnosed and they included failure of formation of an embryo recorded in 14 (28%) of cases, failure of implantation in 18 (36%) and failure of growth and development of the fertilized ovum or the implanted embryo in 9 (18%) cases. Significant management could be recorded in 69.6% of cases managed as failed ovum picking compared to 29.6% in the rest of cases managed as unexplained infertility ($P < 0.005$). In the same way the other causes were significantly managed and cured by managing the related cause and not empirically as unexplained infertility.

Conclusions: Failed ovum picking by the tube, failure of formation of an embryo, failure of implantation and failure of embryo growth could be identified clinically as causes of unexplained infertility. Successful management was encountered more in the cases specifically treated for the identified cause and not generally as cases of unexplained infertility.

Keywords: Unexplained infertility, failed ovum picking, inaccessible ovulation site, ovarian drilling in an accessible site

Introduction

Unexplained infertility is not a rare item of infertility. Approximately 15% to 30% of infertile couples will be diagnosed with unexplained infertility after their diagnostic workup [1]. In unexplained infertility abnormalities are likely to be present but not detected by current methods including semen analysis in the man, assessment of the state of ovulation, ovulation reserve and patency of uterine tubes in the woman [2]. The possible causes of that problem may be commonly certain defect in the sperms and/or ova or in the act of ovulation or ovum picking by the tube or the act of fertilization or implantation or other subclinical general and/or immunological causes [3,4]. Most of the local causes were actually suggested causes and were difficult to be diagnosed clinically and to be specifically managed. Ovum picking by the fimbrial end of the tube is an essential step in the occurrence of pregnancy. The actual mechanism of this process and its clinical identification and

methods used for diagnosing defects in this process were not actually known. This process may be an important cause of unexplained infertility. The author, in a previous study [5], could prove the presence of certain relation between the fimbrial end of the uterine tube and the ovulation site. The author, in that study could also diagnose the occurrence of ovum picking by determining the ability of the fimbrial end of the tube to reach and surround the ovulation site. The latter state was technically proved during laparoscopy and in some cases during laparotomy and was commonly associated with normal fertility. So it was considered indicative of successful ovum picking and was given the name of "tubo-ovarian accessibility test". Recently some other authors could confirm the previous findings and their relation to picking by the tube [6]. Failed ovum picking by the tube was definitely suggested as a cause of unexplained infertility, but strange enough its clinical diagnosis was not known by all the available clinical

techniques. But, salpingography was known to demonstrate the state of the tubes but rarely could demonstrate the state of the fimbrial end which is responsible for the actual ovum picking. Meanwhile, pelvic ovarian sonography can demonstrate the site of the main growing follicle, the site of the corpus luteum, but rarely can it demonstrate the tube-ovarian relation necessary for ovum picking. The combined use of the previous techniques may determine the previous relation and may be used for diagnosis of ovum picking. Similarly, other causes of unexplained infertility as defective fertilization due to defective sperms with or without defective ova, defective implantation and defective development were not easily diagnosed or treated. But it was noticed that failure of certain cases of *in vitro* fertilization may be due to causes similar to the previously mentioned causes especially if the IVF was done for unexplained infertility. Accordingly, the causes of the latter condition may be determined by determining the causes of failure IVF used for managing the latter condition.

Generally many studies showed the treatment for unexplained infertility due to any of the previous causes to be by definition empiric because it does not address a specific defect or functional impairment. Generally management usually includes controlled ovarian hyperstimulation with/ or without timed artificial insemination.

This study is done to determine the efficacy of suggested clinical techniques and operations used for diagnosis and management of the previously suggested causes.

Materials and methods

This study is a prospective controlled diagnostic and operative study. It included 50 unexplained infertility cases and 50 fertile women as controls. In addition, 50 cases of failed IVF done for other cases of unexplained cases were included to determine the possible causes of failed IVF and other causes of unexplained infertility. The studied and control cases were investigated for the possible clinical diagnosis of the tubo-ovarian relation and possibly ovum picking by the tube. Cases were randomly selected and assigned to both the studied groups and controls. The fertile control cases were gynecological cases needed lower abdominal and/or pelvic surgery for conditions as diffuse lower abdominal and/or pelvic pains, enterocele and some cases of appendectomy. The infertile cases were nulligravida nullipara and the fertile cases were multipara 2-4. All cases were 20-35 years old and were selected from the gynecologic clinic at Kasr El Aini School of Medicine, Cairo University, Egypt.

The unexplained infertility was diagnosed according to the gynecological instructions known. The causes of unexplained infertility were diagnosed essentially in two steps. The latter were the state of ovum picking and the other causes related to fertilization, implantation and embryo growth and development. Determining of the latter causes were done by determining the causes of failed IVF done for managing these cases which were the causes also of the unexplained infertility. Meanwhile

the state of ovum picking was clinically diagnosed by the combined use of selective salpingography and ovarian sonography and was proved by laparoscopy and in some cases by laparotomy using the tubo-ovarian accessibility test suggested by the author in a previous study. Successful ovum picking was proved in cases in which the picking end of the tube can reach and cover the ovulation site. Failure of that end of the tube to reach and/ or to cover the ovulation site was commonly associated with failed ovum picking. The selective salpingography was done by special moldable polythene tube and was molded so as its introduction towards the tubal junction will result in its fitting into the utero-tubal junction where the radio-opaque material will be injected gradually in small doses of 0.5 ml each. When the necessary radiological findings were obtained the injection of the radio-opaque material was stopped and the radiological findings were recorded. Then the ovarian sonography (**Figure 1**) was immediately done after the previous procedure to complete the combined imaging in order to determine the site of ovulation and the possible tubal relation to that site. The interstitial, isthmic and ampullary parts of the tube could easily be identified by salpingography. But the fimbriated part of the tube could not easily be identified as the previous parts. But, the fimbriae could be easily identified by the combined imaging technique. The ovulation site was identified clinically by the presence of dominating follicle measuring 18-22 mm or the presence of corpus luteum in that site. Meanwhile the fimbrial end of the tube is identified as radio-opaque area present at the end of the ampullary part of the tube and the fimbriae could be also identified at the same site.

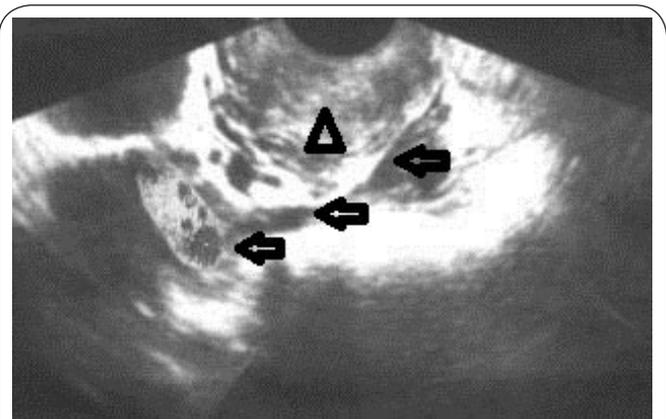


Figure 1. Vaginal hystero-salpingography contrast sonography showing the uterus (arrow head), the tube (arrows), the ovary containg growing follicle surrounded by the tubal fimbriae indicating successful picking of ova by the tube.

The infertile cases having defective ovum picking were divided into two groups; the first included 12 cases and was managed by controlled ovarian hyperstimulation to have other ovulation sites that may be accessible to the fimbrial end of the tube.

Meanwhile the second group included 11 cases and had in addition ovarian drilling in the site accessible to the tubal fimbriae on the assumption that ovulation might occur from that drilled site or near it. The occurrence of successful pregnancy was followed by routine antenatal care. IVF was used in both groups for management of cases failed to have pregnancy during the first 6 months of the previous treatment.

On the other hand, 27 cases of the unexplained infertility identified after failure of the IVF refused further management. Meanwhile, 10 cases were managed by ICSI and 13 cases were managed by ICSI after giving their husbands 50 mg clomiphene citrate for 10 days and ICSI was done in the next week. The latter was given on the assumption that certain defective sperm function may be responsible for the associated cause in these cases.

The Z score was used for statistical evaluation of the different percentages recorded in the different groups studied.

All parts of the research design including the patients and methods, in addition to the results were revised and approved by the Institutional Review Board (IRB).

Results

Unexplained infertility was recorded in 50 (18.3%) of cases among 273 infertility cases attending the outpatient fertility clinic. Ovum picking was expected to occur in all the fertile cases. The latter process could be clinically diagnosed by the combined use of selective salpingography and pelvic ovarian sonography in 90% of the fertile cases. But their actual occurrence as determined in the cases needed laparoscopy or laparotomy was found to be 98% of these cases. Accordingly, missing such finding may be clinically recorded in 8% of these cases. On the other hand positive ovum picking was recorded clinically in 52% only and operatively in 54% of the infertile cases (Figure 2). The latter figures were significantly less than that recorded in the fertile cases ($P < 0.05$). This may draw the attention to the possible role of this factor in the causation of unexplained infertility. The use of the combined clinical techniques for diagnosing the state of ovum picking was found to be essential in these cases as the result of use of each of them separately did not exceed 20% (Table 1).

Failed accessibility of the ovulation site to the fimbrial end of the tube could be diagnosed clinically in 42% of the infertile cases. The corresponding figure in the fertile cases was significantly less ($P < 0.005$) as it is recorded in only 2% of cases (Figure 3). Operatively the corresponding figures were 2% in the fertile cases and 46% in the infertile cases. So missing of the clinical diagnosis of failed ovum picking may occur in 4% of the infertile cases. The state of the tubal fimbriae and its normality could be diagnosed in most of the cases and could be proved to be abnormal in four cases only (Figure 4). The other causes of the unexplained infertility suggested and investigated were failure of formation of an embryo recorded in 14 (28%) of cases and was due to defective sperms and/or ova and due to defective fertilization also. In

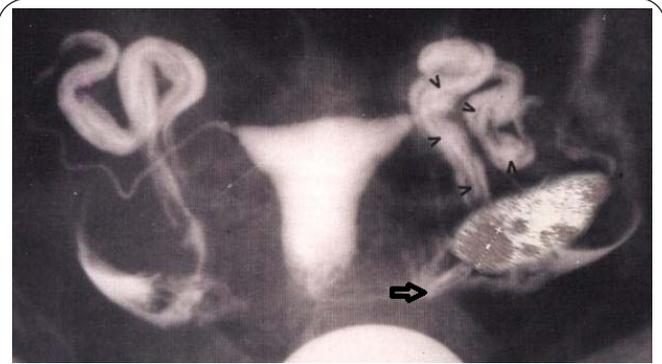


Figure 2. Combined hystero-salpingography and ovarian sonography showing the tubal fimbriae (arrow) surrounding a growing follicle and indicating successful ovum picking. The arrow heads show the site of the tubal cavity.

addition failure of implantation was recorded in 18 (36%) of cases and failure of growth and development of the fertilized ovum or the implanted embryo in 9 (18%) of cases. Failure to determine or to obtain a cause was also recorded in 9 (18%) of these cases (Table 2).

Cases having failed ovum picking were managed by controlled ovarian stimulation and could have 5 (45.5%) successful pregnancies in the first 6 months. Meanwhile controlled ovarian stimulation with ovarian drilling in more accessible site could have 8 (66.7%) successful pregnancies in the same period (Table 3). The latter result was significantly higher than that recorded for the other group managed ($P < 0.05$). Most of the pregnancies occurred in the fourth and fifth months of management. Results showed also that only one case of the second group aborted at the 12th week of pregnancy and one case of the first group delivered prematurely at the 34th week of pregnancy. IVF was tried after failure of the previous management in 10 cases. Three pregnancies were successfully obtained in the latter cases and were continued their pregnancy to the full term pregnancy. Successful pregnancy was collectively obtained in 16 (69.6%) of cases after the successful diagnosis of the failed ovum picking compared to 8 (29.6%) of the rest of cases managed as unexplained infertility. On the other hand, cases had clinically diagnosed causes other than failed ovum picking showed the occurrence of two pregnancies after repeat intra cytoplasmic sperm injection (ICSI) done after three months without sperm activation and the occurrence of 7 pregnancies after sperm activation. Meanwhile, two other pregnancies could be recorded spontaneously in 27 cases refused further management.

Discussion

Unexplained infertility was found to be significant item encountered in 18.3% of the infertility cases attended the outpatient. The studied infertility was considered unexplained because the cause could not be determined by the available techniques.

Table 1. Results of different technique used for diagnosis of ovum picking in 50 fertile cases and 50 (18.3%) of cases of unexplained infertility recorded among 273 infertile cases.

Methods	Laparoscopy and laparotomy	Combined techniques	Ovarian sonography	Selective salpingography
Findings				
Fimbrial end accessible*				
Fertile cases	49 (98%)	45 (90%)	5 (10%)	4 (8%)
Infertile cases	27 (54%)	26 (52%)	4 (8%)	3 (6%)
Fimbrial end not accessible to ovulation site**				
Fertile cases	1 (2%)	1 (2%)	5 (10%)	2 (4%)
Infertile cases	23 (46%)	21 (42%)	4 (8%)	4 (8%)
Finding cannot be identified				
Fertile cases	0 (0%)	4 (8%)	40 (80%)	44 (88%)
Infertile cases	0 (0%)	3 (6%)	42 (84%)	43 (86%)

*Significant high figures recorded by the combined techniques compared to figures recorded by other techniques (P<0.05).

**Significant high figure of failed ovum picking in the infertile cases compared to that recorded in the fertile cases (P<0.005).

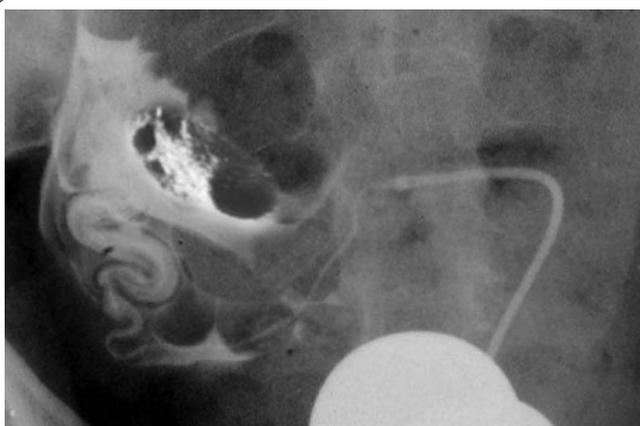


Figure 3. Combined selective salpingography and ovarian sonography showing the ovulation site away from the picking fimbrial end of the tube indicating failed ovum picking. Notice the shape of the fimbrial end which is seen as radio-opaque area following the ampullary part of the tube.

Table 2. Diagnosed causes of unexplained infertility recorded in cases of failed IVF used for managing these cases.

Number and percentage	Number and percentage
Causes of infertility	
Failed formation of fertilized ovum or an embryo due to defective sperms and/or ova	14 (28%)
Failed implantation	18 (36%)
Failed growth and development of the fertilized ovum or the implanted fertilized ovum	9 (18%)
Undetermined causes	9 (18%)
Total	50 (100%)

Accordingly the adopted management suggested for these cases was not specific for certain cause but empirically for all

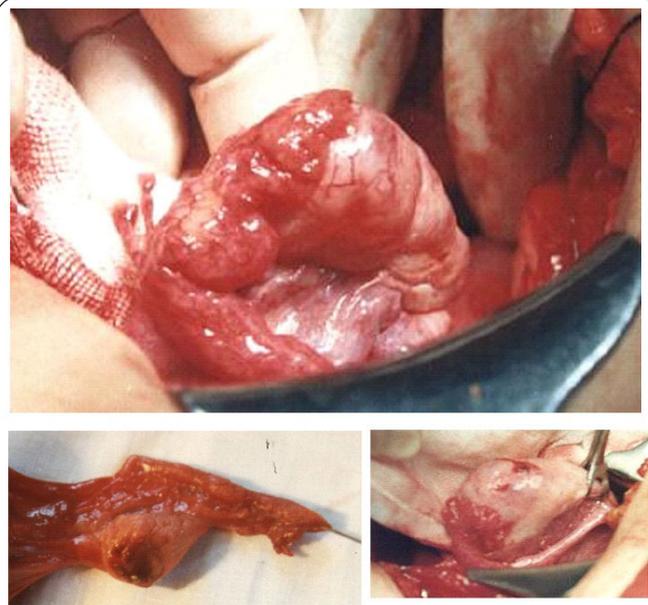


Figure 4. The state of ovum picking as seen by laparoscopy and laparotomy. The upper picture shows the fimbrial end of the tube covering the ovulation site completely resulting in successful ovum picking. The lower left picture shows abnormality of the fimbrial end of the tube which is shorter and has defective fimbriae. The lower right picture showed stimulated ovary with two ovulation sites not accessible to the fimbriae and one accessible and completely covered by the fimbriae.

possible causes. The present study was planned for obtaining proper clinical diagnosis of the causes and to have the specific and proper management of these causes. Two methods of diagnosis were actually selected for diagnosis of these cases. These included clinical imaging of the tubo-ovarian relation by combined selective salpingography and ovarian sonography and the diagnosis of other causes by identification of causes of

Table 3. Results of management of 23 cases out of 50 of unexplained infertility due to failed ovum picking and 27 cases managed empirically and 23 cases due to other causes.

Cases and significance	Number and percentage of pregnancies	Number and percentage of cases
Type of management		
Management of failed ovum picking		
Controlled ovarian stimulation	5 (45%)	11 (47.8%)
Controlled ovarian stimulation and accessible ovarian drilling*	8 (66.7%)	12 (52.2%)
Total	13 (56.5%)	23 (100%)
IVF	3 (33.3%)	10 (100%)
Total**	16 (69.6%)	23 (46%)
Empirical management of cases not having failed ovum picking	8 (29.6%)	27 (54%)
Management of cases having other causes		
Spontaneous pregnancies without treatment	2 (7.4%)	27 (54%)
Repeat ICSI without testicular stimulation	2 (20%)	10 (20%)
Repeat ICSI after testicular stimulation***	7 (53.8%)	13 (26%)
Total	11 (47.8%)	23 (100%)

*Significant higher percentage of cure compared to other two lines of treatment ($P < 0.005$).

**Significant higher percentage of pregnancies compared to the empirically managed cases ($P < 0.005$) and managed cases of unexplained infertility due to other causes ($P < 0.05$).

***Significantly higher percentage of pregnancies compared to cases treated by the other method without testicular stimulation ($P < 0.05$).

failure of IVF done for management of similar cases. In addition, the state of tubo-ovarian relation was usually determined by laparoscopy or during laparotomy before the actual surgery suggested was done.

Results showed the failed ovum picking to be the commonest of the investigated causes of unexplained infertility. The high local incidence recorded in these cases may be due to the fact that ovulation occurs from different sites of the ovary which is known to be equally accessible and inaccessible to the picking fimbrial end of the tube. In addition the high incidence may be also secondary to the availability methods of diagnosis of that cause more than the other causes. It may be of interest to know that, the presence of condition as persistence failure of ovum picking may draw the attention to the possible presence of fixed ovulation site for each normal ovulating ovary. On the other hand, failed fertilization and

failed implantation were found to be the main causes of failed IVF used for managing these cases and the main causes of unexplained infertility in these cases also. The clinical use, advantages and disadvantage of the previous techniques used for diagnosis of ovum picking were identified by other authors [7,8]. But most of these studies which included the identification of these diagnostic techniques, if not all of them were used essentially for determining the tubal patency. But, none of them attempted their use in the clinical detection of the tubo-ovarian relation or in determining the state of ovum picking [9,10]. In addition defective ovum picking may be also present in cases having anatomically defective fimbriae. Defective fimbriae were known to be unnoticed and undiagnosed. So, they were considered common causes of unexplained infertility. Recently some authors could identify and refer to these defects [11], but their clinical diagnosis were rarely identified or included. The state of the fimbrial end of the tube and the ovulation site must be specially determined and included during the investigation of unexplained infertility and must be also included in the investigation of infertility in general.

The main diagnostic problems encountered in the clinical diagnosis of that condition by each of the previous techniques were the difficulty in identification of some parts and organs involved in that procedure. But, the use of the double technique could overcome the problems recorded by the previously used techniques. These problems included identification of the picking end of the tube, the ovulation site and the ability of the picking tubal end to reach and cover the ovulation site. The fimbrial end of the tube was found to be the part of the tube following the ampullary part and was directly related to the ovary. In addition, it was seen as radio-opaque area present distal to the ampullary part of the tube and fimbriae could commonly be seen related to that part. Meanwhile the ovulation site was identified by the presence of growing follicle or corpus luteum at that site. Cases having normal tubal fimbriae and tubo-ovarian accessibility were found to be usually fertile cases. Meanwhile absence of that accessibility and/or defective fimbriae were commonly associated with unexplained infertility most probably due to failed ovum picking [12]. Rarely the tube may pick the ova directly from the surface of the ovary away from the ovulation site or even from the peritoneal or the pelvic cavity. This could be recorded in one case of the fertile cases of the present study. The diagnosis after the failure of IVF used for managing some of these cases was usually accurate and beneficial but it was found to be late diagnosis and may be considered expensive in some cases. In addition, the cause was usually not obtained in the cases responded to the IVF management but, the resulted pregnancy was not continued or completed.

In the present study management was essentially done by controlled hyperstimulation of the ovary to produce ova that may be accessible for picking. Intrauterine insemination was not included in these cases to obtain proper determination of

the role of ovarian hyperstimulation in managing these cases. Ovarian hyperstimulation without intrauterine insemination was also suggested and tried by other authors and results were nearly comparable [13]. Identification of a cause and its management was found to be associated with high incidence of cure. The proximal ovarian drilling suggested by the first author was found to produce ova more accessible to the picking end of the uterine tube. Also ovarian and testicular activation usually resulted in pregnancies due to the production of more active and normal ova and sperms that may be necessary for successful IVF and ICSI. Successful management was recorded in 56.5% of cases managed as suggested by the authors for failed ovum picking, meanwhile it was recorded in 29.6% of cases managed as unexplained infertility. Similarly, successful management was recorded in 53.8% of cases after testicular stimulation and in 20% not used any testicular stimulation in the cases diagnosed to have other causes of unexplained infertility. Pregnancies produced in these cases occurred in the fourth and fifth months of management. Accordingly, management should be included minimally for six months and not for only three months as suggested by some other authors [14].

Conclusion

This study could significantly diagnose some causes of unexplained infertility. These were clinically obtained by retrospective identification of the causes of failed IVF used for managing such case and by combined selective salpingography and ovarian sonography. In addition, ovarian drilling in an accessible ovarian site and ovarian and testicular hyperstimulation were suggested as methods of management of the diagnosed causes.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	SMT	AHA	FMAW
Research concept and design	✓	--	--
Collection and/or assembly of data	✓	✓	✓
Writing the article	✓	--	--
Critical revision of the article	✓	--	--
Final approval of article	✓	✓	--
Statistical analysis	✓	✓	--

Acknowledgement

We acknowledge and thank all patients participated in this study.

Publication history

EIC: Christos Iavazzo, Royal Surrey County Hospital, UK.
 Received: 04-Feb-2014 Accepted: 27-May-2014
 Published: 28-Jun-2014

References

1. Ray A, Shah A, Gudi A and Homburg R. **Unexplained infertility: an update and review of practice.** *Reprod Biomed Online.* 2012; **24**:591-602. | [Article](#) | [PubMed](#)
2. **The Practice Committee of the American Society for Reproductive**

3. Randolph JF, Jr. **Unexplained infertility.** *Clin Obstet Gynecol.* 2000; **43**:897-901. | [Article](#) | [PubMed](#)
4. Barbieri RL. **The initial fertility consultation: recommendations concerning cigarette smoking, body mass index, and alcohol and caffeine consumption.** *Am J Obstet Gynecol.* 2001; **185**:1168-73. | [Article](#) | [PubMed](#)
5. Ahmad-Thabet SM. **The fimbrio-ovarian relation and its role on ovum picking in unexplained infertility: the fimbrio-ovarian accessibility tests.** *J Obstet Gynaecol Res.* 2000; **26**:65-70. | [Article](#) | [PubMed](#)
6. Heikkinen H, Tekay A, Volpi E, Martikainen H and Jouppila P. **Transvaginal salpingosonography for the assessment of tubal patency in infertile women: methodological and clinical experiences.** *Fertil Steril.* 1995; **64**:293-8. | [Article](#) | [PubMed](#)
7. Strandell A, Bourne T, Bergh C, Granberg S, Asztely M and Thorburn J. **The assessment of endometrial pathology and tubal patency: a comparison between the use of ultrasonography and X-ray hysterosalpingography for the investigation of infertility patients.** *Ultrasound Obstet Gynecol.* 1999; **14**:200-4. | [Article](#) | [PubMed](#)
8. Thurmond AS, Machan LS, Maubon AJ, Rouanet JP, Hovsepian DM, Moore A, Zagoria RJ, Dickey KW and Bass JC. **A review of selective salpingography and fallopian tube catheterization.** *Radiographics.* 2000; **20**:1759-68. | [Article](#) | [PubMed](#)
9. Meldrum DR, Chetkowski RJ, Steingold KA and Randle D. **Transvaginal ultrasound scanning of ovarian follicles.** *Fertil Steril.* 1984; **42**:803-5. | [Article](#) | [PubMed](#)
10. Exacoustos C, Zupi E, Carusotti C, Lanzi G, Marconi D and Arduini D. **Hysterosalpingo-contrast sonography compared with hysterosalpingography and laparoscopic dye pertubation to evaluate tubal patency.** *J Am Assoc Gynecol Laparosc.* 2003; **10**:367-72. | [Article](#) | [PubMed](#)
11. Siddhartha CH, Rajib GC, Sandip D, and Vishnu P. **Minor tubal defects—The unnoticed causes of unexplained infertility.** *J Obstet Gynaecol.* 2010; **60**:331-336. | [Article](#)
12. Kumar A.V and Decharney AH. Evaluation of female: Tubal factor in cedars M. I ed. *Infertility: New Delhi, Tata Mc Graw-Hill* 2005:35-46.
13. Chung CC, Fleming R, Jamieson ME, Yates RW and Coutts JR. **Randomized comparison of ovulation induction with and without intrauterine insemination in the treatment of unexplained infertility.** *Hum Reprod.* 1995; **10**:3139-41. | [Article](#) | [PubMed](#)
14. Aboalghar M, Mansour R, Serour G, Abdrazek A, Amin Y and Rhodes C. **Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials.** *Fertil Steril.* 2001; **75**:88-91. | [Article](#) | [PubMed](#)

Citation:

Thabet SMA, Ali AH and Wousabi FMA. **Diagnosis and management attempts of some causes of unexplained infertility.** *Gynecol.* 2014; **2**:2.
<http://dx.doi.org/10.7243/2052-6210-2-2>