Glenn L. Schattman
Sandro C. Esteves
Ashok Agarwal *Editors*

Unexplained Infertility

Pathophysiology, Evaluation and Treatment

Springer

Unexplained Infertility

Glenn L. Schattman • Sandro C. Esteves
Ashok Agarwal
Editors

Unexplained Infertility

Pathophysiology, Evaluation and Treatment

Springer

Editors
Glenn L. Schattman
Ronald O. Perelman and Claudia Cohen Center
for Reproductive Medicine
Weill Cornell Medical College
New York, NY, USA

Sandro C. Esteves
ANDROFERT, Andrology and Human
Reproduction Clinic
Referral Center for Male Reproduction
Campinas, São Paulo, Brazil

Ashok Agarwal
Lerner College of Medicine
Case Western Reserve University
Andrology Center &
Center for Reproductive Medicine
Cleveland Clinic
Cleveland, OH, USA

ISBN 978-1-4939-2139-3 ISBN 978-1-4939-2140-9 (eBook)
DOI 10.1007/978-1-4939-2140-9

Library of Congress Control Number: 2014955347

Springer New York Heidelberg Dordrecht London
© Springer Science+Business Media, LLC 2015
This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Contents

Potential Etiologies of Unexplained Infertility in Females

13

Daniela Galliano and Antonio Pellicer

Introduction

Infertility is defined as a failure to conceive after an interval of approximately 12 months of regular and unprotected intercourse [1]. An estimated 4–17% of couples seek medical treatment to resolve their infertility, but it is generally accepted that there are more cases unreported [2]. Therefore, infertility remains both prevalent and problematic among couples worldwide [3].

Unexplained infertility (UI) is said to be unexplained when a couple fails to conceive after 12 months of regular and unprotected intercourse and in the absence of any identified abnormalities with an incidence of approximately 15–30% [1, 4, 5]. This incidence may vary depending on the population studied and the criteria used to make the diagnosis. UI has no identified pathophysiologic basis and, as such, is a diagnosis of exclusion that should be made after a thorough but time-efficient investigation of the couple is performed, [6] including a semen analysis, assessment of ovulation, evaluation of tubal patency by hysterosalpingogram (HSG), or laparoscopy (LPS) [7] and, if indicated, tests for ovarian reserve.

UI may be a multifactorial disorder of reproduction [8] and if so, it is unlikely that all the etiologies involved could be diagnosed even after a meticulous evaluation [9], with many suspected etiologies without definitive diagnostic methods or criteria. However, significant improvements in diagnostic tools and assisted reproductive technology (ART) treatments have led to the finding of many causes of infertility that in the past have only been suspected, but now are well known. Poor embryo development and quality may be identified in the ART lab or if further testing is performed, chromosomal aneuploidies may be revealed by preimplantation genetic screening (PGS).

On these grounds, the validity of the term "unexplained infertility" has been doubted by some authors and they propose to substitute the term "unexplained" with "undiagnosed" [10], since UI seems to be sensitive to the number and quality of the tests performed. Indeed, data from a study by Taylor and Collins showed that the percentage of couple with UI decreases as the number of diagnostic tests increases, from 22% in studies published prior to 1960 to 14% in studies published after 1980 [11]. Additionally, the difference in diagnosis may be related to the duration of infertility prior to seeking treatment (which may have been longer in the earlier studies as there was little intervention possible), and just on the number of diagnostic tests used.

Nonetheless, despite improvements in the diagnosis and treatment of reproductive disorders, at the present time many couples still have no explanation for their infertility [12], as posed by Southam in 1960 [13].

UI should not be regarded as a permanent condition but rather a relative incapacity to conceive, and as such, it would be better considered as subfertility [1], since time may lead these couples to achieve pregnancy without treatment. In fact, it has been estimated that approximately 40–60% of couples with UI will spontaneously conceive within 3 years [14], with the duration of infertility and the age of the female partner being the most important prognostic factors [15]. Furthermore, the outcomes of ART treatment for idiopathic infertility are promising [6–8, 16].

Possible Etiologies of UI in Females

As far as is known and after a thorough evaluation, the etiologies below appear to be potential causes of UI. These include ovarian, tuboperitoneal, uterine, and embryonic factors (Fig. 13.1).

D. Galliano (✉) · A. Pellicer
Department of Reproduction, Instituto Valenciano Infertilidad (IVI), Ronda General Mitre (Pza. Bellanes), 14, 08017 Barcelona, Spain
e-mail: Daniela.Galliano@ivi.es

G. L. Schattman et al. (eds.), *Unexplained Infertility*, DOI 10.1007/978-1-4939-2140-9_13,
© Springer Science+Business Media, LLC 2015

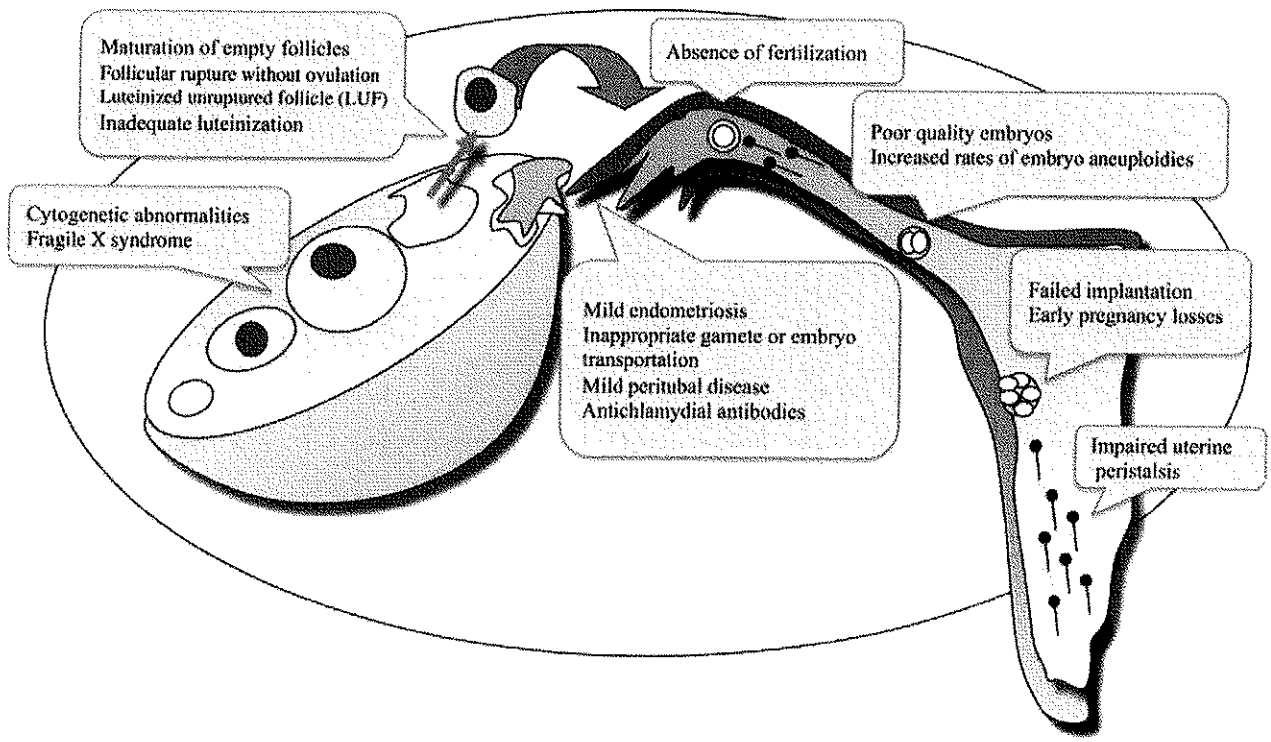

Fig. 13.1 Possible etiologies of UI in females: abnormal ovarian folliculogenesis, ovulatory dysfunction, tuboperitoneal disorders, impaired fertilization, abnormal embryo development, abnormal endometrial receptivity, and altered sperm transport due to impaired uterine peristalsis

Abnormal Ovarian Folliculogenesis

UI can occur, even in the presence of regular menstrual cycles, as a result of diminished ovarian reserve, defined as a reduced quantity and quality of the remaining population of primordial follicles within the ovary than would be expected for a given chronological age. Even though chronological age is the most important determinant of ovarian reserve, evidence has shown great variability in the rate of ovarian ageing [17]. Therefore, women with prematurely ageing ovaries (PAO) [18] may be mistakenly diagnosed with UI, since nobody would expect such fertility decline be based on their age alone.

In this setting, female fertility loss may be assessed by tests of ovarian reserve, such as day 3 serum follicle stimulating hormone (FSH), anti-Müllerian hormone (AMH) levels, and antral follicle count (AFC) [19]. FSH and AMH do not measure the same ovarian reserve parameters. Indeed, FSH is mostly representative of the last 2 weeks of follicular maturation when follicles come to be gonadotropin-sensitive [20], while AMH, exclusively produced by the granulosa cells of early antral and preantral follicles, mainly reflects the earlier stages of folliculogenesis [21, 22, 23]. AFC, visualized by transvaginal ultrasound, is considered the best predictor of ovarian response to stimulation [24], since it correlates with the number of oocytes retrieved and ART outcomes in terms of ongoing pregnancy [25, 26].

In this context, ovarian reserve testing and genetic screening could be of great importance, especially in women <35 years old, to reveal cytogenetic abnormalities, as in the case of the Fragile X syndrome (FXS), that is caused by an increased number of trinucleotide (CGG) repeats on the fragile X (FMR1) gene and linked to premature ovarian failure [27].

Such genetic and ovarian reserve screening may help women potentially have some knowledge about the duration of their own reproductive window and help clinicians counsel patients and direct them to an appropriate treatment option, which in some cases may include gamete donation [19].

Ovulatory Dysfunction

Several abnormalities of ovulation can occur at the gonadal level, such as rupture of the follicle without release of the oocyte, maturation of an empty follicle that does not contain an oocyte, ovulation with inadequate luteinization, incomplete maturation of a follicle resulting in atresia, and finally luteinization of a follicle, under the action of luteinizing hormone (LH), without its rupture and with entrapment of the oocyte, which is also called the luteinized unruptured follicle (LUF)

syndrome [28]. This ovulatory dysfunction is considered as a potential cause of female UI [29, 30] and has been linked to endometriosis and pelvic adhesions [31]. Many publications have appeared since 1978 to describe this syndrome, but the exact mechanism by which the ovulatory follicle fails to rupture is not clearly known. Different mechanisms have been suggested for this syndrome, such as a chronic follicular inflammatory-like reaction involving inhibition of synthesis of prostaglandins [32], luteal phase defect [33] or a primary granulosa cell defect [34].

LUF is characterized by normal endocrine signs of ovulation, such as secretory endometrium, normal production of progesterone, and duration of the luteal phase [20], and is usually diagnosed by ultrasound demonstration of a follicle that does not change in size or consistency after ovulation should have occurred [35]. LUF has been demonstrated in both spontaneous and stimulated cycles [36] and it is estimated to be present in 6–12% of cases of female subfertility and in 20–25% of cases when ovarian stimulation is used [37], but the incidence varies depending on the methods of diagnosis such as LPS or ultrasound or steroid hormone concentrations in peritoneal fluid [38]. Qublan et al. found the recurrence rate of LUF increased from 25% in the first cycle of intrauterine insemination (IU) to 78 and 90% in the second and third cycle, respectively [25]. These data are consistent with those reported by others [23–26], but in contrast to previous studies in which LUF was associated with no recurrence rate in subsequent cycles [39, 40].

Tuboperitoneal Disorders

It has been shown that mild endometriosis can affect normal tubal function, as well as other reproductive processes and since this diagnosis is clinically frequently missed, it may represent a possible etiology of UI. For this reason, diagnostic LPS could be considered as an integral part of the evaluation, and the role of tubal function, not just patency should not be underestimated [41].

The prevalence of endometriosis among women who underwent LPS for an infertility evaluation has been reported to be in the range of 10 [10]–50% [42]. Even if performed by experienced laparoscopists, the diagnosis of subtle endometriosis can be hard to make because the disease is often microscopic and presents with atypical lesions [43, 44], and as such may be underdiagnosed.

Evidence shows that endometriosis may also affect IVF outcomes [45, 46] interfering with many aspects of the process, including follicular development, oocyte retrieval, fertilization and embryo development [47, 48], distortion of adnexal anatomy and creating an adverse peritoneal environment characterized by increased inflammatory cytokines, oxidative stress [22, 49, 50, 51], and augmented number of peritoneal fluid macrophages [52–54]. If endometriosis does so in vitro, it can be expected to have similar effects in vivo leading to impaired conception [5]. Studies have demonstrated that, even in mild cases of endometriosis, pregnancy outcomes may have been affected by subtle tubal abnormalities [55, 56], thus reflecting microscopic endometriosis in the fallopian tubes, which can never be totally excluded, even by LPS [19–20]. Furthermore, data on patients undergoing LPS for infertility indicate that of those who have no macroscopic endometriosis at LPS, at least 6% have microscopic lesions [57, 58] and thus confirms how this diagnosis, especially in patients with infertility may be underestimated [59].

The fallopian tubes play an important role in sperm transport, oocyte capture and transport, fertilization, and early embryo development [60]. Abnormalities in any one of these functions cause defective transport of the oocyte and impaired fertilization, through alterations in tubal peristaltic or ciliary activity [61], which may affect one or both fallopian tubes.

Tubal function can be abnormal despite documentation of tubal patency [62, 63], but HSG has limited value in evaluating tubal function and peritubal disease [64, 65] and may be less accurate in detecting tubal disease than LPS [66, 67]. Moreover, a study performed in an infertile population showed that HSG missed at least one tubal abnormality in 84% of the cases [68]. Despite all these limitations, HSG represents the first line tool to evaluate tubal status, because of its safety and low cost. LPS remains the gold standard for the evaluation of mechanical factors affecting the fallopian tubes, but it can miss proximal disease [65] and cannot be used to directly observe the ampulla, where the fertilization between oocyte and sperm occurs. This may be explored by salpingoscopy. Some researchers think that salpingoscopy could be informative in patients with UI, since it can identify nonobstructive tubal diseases such as fibrosis, adhesions, debris, and foreign bodies [69].

Furthermore, the impact of chlamydial infection in the etiology of tubal pathology secondary to salpingitis [70–72] on female fertility is well documented. Although neither HSG or LPS may identify tubal pathology secondary to chlamydial infections in the absence of overt occlusion or peritubal adhesions, subfertile women with a positive Chlamydia trachomatis antibody have lower chances for pregnancy than seronegative women [73]. This evidence confirms the validity of assessment for chlamydial serology in women under fertility investigation [74, 75].

Impaired Fertilization

A decrease in fertilization has been documented in IVF cycles performed in couple with UI, suggesting gamete defects as potential causes of UI.

Absence of fertilization has been shown in a prospective study from Ruiz et al. [76], in couples with UI and mild endometriosis undergoing IVF/ICSI after four failed intrauterine insemination cycles. It has been found that 11.4% of these couples suffered fertilization failure with standard IVF, and if ICSI would not have been employed, they might have had no embryos available for transfer. In this study, ICSI did not increase fertilization rates over standard IVF in case of UI, but avoided complete fertilization failure in those patients.

Albughar et al. [77] reached similar conclusions with regards to gamete dysfunction in couples with UI, in which the rate of fertilization failure was 22.7%, very similar to those observed in other studies in couples with UI [78, 79].

Abnormal Embryo Development

The use of assisted reproductive techniques has been important not only for therapeutic reasons, but also because it helps to understand the complex process that leads to conception in a given couple. Indeed, it is noteworthy that there is a high incidence of chromosomal abnormalities in human embryos cultured in vitro [80] and that many repetitive implantation failure (RIF) cases are due to embryonic defects, including chromosomal aneuploidy, which increase with maternal age [81] and with the number of previous failed IVF cycles [82, 83]. Different therapeutic options have been proposed to improve the outcome of these patients, including assisted zona hatching [84] and coculturing embryos to the blastocyst stage [85]. However, other studies have found dramatic declines in implantation and pregnancy rates using blastocyst culture in RIF patients due to the limited development of these embryos in extended culture [86].

In a randomized controlled trial of infertile couples with RIF and prior transfers of good-quality embryos, Rubio et al. reported a trend towards an increased incidence of genetic abnormalities in embryos from these couples and an improvement in live-birth rates per transfer by selection of the healthiest embryos with PGS, highlighting the mechanisms of action by which chromosomal abnormalities can have an impact on UI.

Abnormal Endometrial Receptivity

An altered endometrial receptivity may interfere with apposition, adhesion, or penetration of the embryo and results in a failed implantation [87].

Since the 1950s, traditional histologic evaluation of the endometrium performed by pathologists, has been used as a predictor of endometrial receptivity [88, 89], the clinical relevance and reproducibility of which has been questioned in randomized studies [90, 91]. The development of microarray technology [92] helped to analyze the expression of thousands of genes at the same time in an endometrial sample of development in the peri-implantation period. On those grounds, and consistent with the findings that endometrial receptivity may be related to its transcriptomic profile, molecular assessment of endometrial receptivity has been developed [93, 94], a molecular diagnostic tool that contains 238 expressed genes coupled to a computational predictor, which is able to identify endometrial samples within the window of implantation, independent of their histological appearance. The endometrial receptivity array (ERA) test may help to identify patients with implantation failure caused by a nonreceptive endometrium, improving the ability to control the endometrial environment for implantation. Moreover, an endometrial database (EDB) (http://www.endometrialdatabase.com) has been created to facilitate the exchange of information on the genomics of endometrial receptivity, for the improvement of knowledge in this field worldwide [95].

UI may reflect a malfunction of the endometrial-embryo "dialogue" in the early phases of implantation that leads to early pregnancy loss (EPL), or biochemical pregnancy (BP) which could be erroneously interpreted as a failure to conceive. EPL or BP are defined as increases in beta-human chorionic gonadotropin (B-hCG) at the end of the luteal phase due to embryonic implantation that does not result in a clinical pregnancy. The development of sensitive immunoassays for the detection of urinary B-hCG has allowed for detection of a pregnancy within a few days of embryo implantation, which shows high rates of BP in spontaneous conception [96]. Moreover, data from patients who have undergone ART and PGS show that many preclinical implantation failures are due to chromosomal alterations and are found in high rates in natural (25%) [97] and ART conceptions (40%) [98]. Chromosomal aberrations are probably not the only cause of EPL. Indeed, an altered endometrial receptivity due to environmental factors, such as age and excessive ovarian stimulation in IVF cycles, may also play an important role in the etiologies of this disorder, as shown by Troncoso et al. [99].

Altered Sperm Transport due to Impaired Uterine Peristalsis

There is clear evidence that sperm transport through the female genital tract from the cervix into the tubes, assisted by cervico-fundal uterine peristaltic contractions [100, 101], is altered in patients with UI and endometriosis which results in impaired uterine contractility, documented by hysterosalpingoscintigraphy (HSSG) [102]. Data have shown that endometriosis is associated with uterine hyperperistalsis and dysperistalsis, which may cause impaired or total failure in sperm transport capacity respectively, especially when diffuse adenomyosis is also detected [103]. Dysperistalsis is

associated with reduced natural conception rates [104, 105] and consequently IVF/ICSI may be required even in couples with otherwise patent fallopian tubes and normal semen parameters.

Conclusions

Infertility is unexplained after thorough evaluation in about 15–30 % of cases and constitutes a multifactorial disorder of reproduction, as discussed in this chapter. Many potential etiologies of UI have been proposed here, including ovarian factors, fertilization failure, failure of the embryo to develop, failure of implantation and impaired or total failure in oocyte and sperm transport due to altered tubal and uterine function.

Increasingly, complex ART options have led to the finding of many causes of infertility that in the past have only been suspected, but can now be diagnosed, as in the case of chromosomal aneuploidies identified with PGS. However, multiple potential etiologies of UI could coexist with identified causes for infertility and therefore many couples with identified factors may fail to conceive despite receiving appropriate treatment for the identified causes. It is, therefore, imperative to perform a complete and thorough evaluation of the infertile couple, including evaluation for these subtle etiologies, even in couples whose infertility evaluation has revealed a potential etiology.

References

1. Evers JL. Female subfertility. Lancet. 2002;360:151–9.
2. Gnoth C, Godehardt E, Frank-Herrmann P, Friol K, Tigges J, Freundl G. Definition and prevalence of subfertility and infertility. Hum Reprod. 2005;20:1144–7.
3. Hamada A, Esteves SC, Nizza M, Agarwal A. Unexplained male infertility: diagnosis and management. Int Braz J Urol. 2012;38(5):576–94
4. The Practice Committee of the American Society for Reproductive Medicine, authors. Effectiveness and treatment for unexplained infertility. Fertil Steril. 2006;86(5 suppl):S111–S4.
5. Smith S, Pfiefer SM, Collins J. Diagnosis and management of female infertility. JAMA. 2003;290:17.
6. Quaas A, Dokras A. Diagnosis and treatment of unexplained infertility. Rev Obstet Gynecol. 2008;1(2):69–76.
7. The Practice Committee of the American Society for Reproductive Medicine, authors. Optimal evaluation of the infertile female. Fertil Steril. 2006;86(5 suppl):S264–S7.
8. Marrero MA, Ory SJ. Unexplained infertility. Curr Opin Obstet Gynecol. 1991;3(2):211–8.
9. Collins JA, Crosignani PG. Unexplained infertility: a review of diagnosis, prognosis, treatment efficacy and management. Int J Gynaecol Obstet. 1992;39:267.
10. Gleicher N, Barad D. Unexplained infertility: does it really exist? Hum Reprod. 2006;21:1951–1955.
11. Taylor PJ, Collins JA. Unexplained infertility. New York: Oxford University Press; 1992. p. 153–69.
12. Isaksson R, Tiitinen A. Present concept of unexplained infertility. Gynecol Endocrinol. 2004;18(5):278–90.
13. Southam A. What to do with the "normal" infertile couple. Fertil Steril. 1960;11:543–9.
14. Collins JA, Burrows EA, Willan AR. The prognosis for live birth among untreated infertile couples. Fertil Steril. 1995;64:22.
15. Collins J, Rowe T. Age of the female partner is a prognostic factor in prolonged unexplained infertility: a multicenter study. Fertil Steril. 1989;52:15.
16. Templeton AA, Penney GC. The incidence, characteristics and prognosis of patients whose infertility is unexplained. Fertil Steril. 1982;37:175–82.
17. te Velde ER Pearson PL. The variability of female reproductive ageing. Hum Reprod Update. 2002;8:141–54.
18. Gleicher N, Weghofer A, Oktay K, Barad D. Do etiologies of premature ovarian aging (POA) mimic those of premature ovarian failure (POF)? Hum Reprod. 2009;24(10):2395–400.
19. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update. 2006;12(6):685–718.
20. Wolff E, Taylor H. Value of the day 3 follicle-stimulating hormone measurement. Fertil Steril. 2004;81:1486–8.
21. Feyereisen E, Méndez Lozano DH, Taieb J, Hesters L, Frydman R, Fanchin R. Anti-Müllerian hormone: clinical insights into a promising biomarker of ovarian follicular status. Reprod Biomed Online. 2006;12:695–703. doi:10.1016/S1472–6483(10)61081-4.
22. Gleicher N, Weghofer A, Barad DH. Discordances between follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH) in female infertility. Reprod Biol Endocrinol. 2010;8:64. doi:10.1186/1477-7827-8-64.
23. Visser JA, de Jong F, Laven J, Themmen A. Anti-Müllerian hormone: a new marker for ovarian function. Reproduction. 2006;131:1–9.
24. Hendriks DJ, Kwee J, Mol BW, te Velde ER, Broekmans FJ. Ultrasonography as a tool for the prediction of outcome in IVF patients: a comparative meta-analysis of ovarian volume and antral follicle count. Fertil Steril. 2007;87(4):764–75.
25. Frattarelli JL, Levi AJ, Miller BT, Segars JH. A prospective assessment of the predictive value of basal antral follicles in in vitro fertilization cycles. Fertil Steril. 2003;80(2):350–5.
26. Devroey P, Fauser B, Diedrich K. Approaches to improve the diagnosis and management of infertility. Hum Reprod Update. 2009;15(4):391–408.
27. Wittenberger MD, Hagerman RJ, Sherman SL et al. The FMR1 premutation and reproduction. Fertil Steril. 2007;87:456–65.
28. Katz E. The luteinized unruptured follicle and other ovulatory dysfunctions (Review). Fertil Steril. 1998;50(6):839–50.
29. Hamilton CJ, Wetzels LC, Evers JL, Hoogland HJ, Muitjens A, De Haan J. Follicle growth curves and hormonal patterns in patients with the luteinized unruptured follicle syndrome. Fertil Steril. 1985;43:541–8.
30. Koninckx PR, Brosens IA. Clinical significance of the luteinized unruptured follicle syndrome as a cause of infertility. Eur J Obstet Gynecol Reprod Biol. 1982;13:355–68.
31. Marik J, Hulka J. Luteinized unruptured follicle syndrome: a subtle cause of infertility. Fertil Steril. 1978;29:270–4.
32. Murdoch WJ, Cavender JL. Effect of indomethacin on the vascular architecture of preovulatory ovine follicle: possible implication in the luteinized unruptured follicle syndrome. Fertil Steril. 1989;51:153–5.
33. Kugu K, Taketani Y, Kohda K, Mizuno M. Exaggerated prolactin response to thyrotopin-releasing hormone in infertile women with the luteinized unruptured follicle syndrome. Arch Gynecol Obstet. 1991;249:27–31.
34. Zaidi J, Jurkovic D, Campbell S, Collins W, McGregor A, Tan SL. Luteinized unruptured follicle: morphology, endocrine function and blood flow changes during the menstrual cycle. Hum Reprod. 1995;10:44–9.

35. Liukkonen S, Koskimies AI, Tenhunen A, Ylöstalo P. Diagnosis of luteinized unruptured follicle (LUF) syndrome by ultrasound. Fertil Steril. 1984;41(1):26–30.
36. Craft I, Shelton K, Yovich L, Smith D. Ovum retention in the human. Fertil Steril. 1980;34:537–41.
37. Qublan H, Amarin Z, Nawasreh M, Diab F, Malkawi S, Al-Ahmad N, Balawneh M. Luteinized unruptured follicle syndrome: incidence and recurrence rate in infertile women with unexplained infertility undergoing intrauterine insemination. Hum Reprod. 2006;21(8):2110–3. (Epub 2006 Apr 13).
38. Temmerman M, Devroey P, Naaktgeboren N, Amy JJ, Van Steirteghem AC. Incidence, recurrence and treatment of the luteinized unruptured follicle syndrome. Acta Eur Fertil. 1984;15:179–83.
39. Aksel S. Thou shall not luteinize nor rupture. Fertil Steril. 1987;47:762–4.
40. Luciano AA, Peluso J, Koch E, Maier D, Kuslis S, Davison E. Temporal relationship and reliability of the clinical, hormonal, and ultrasonographic indices of ovulation in infertile women. Obstet Gynecol. 1990;75:412–6.
41. Bérubé S, Marcoux S, Langevin S, Maheux R. Canadian Collaborative Group on Endometriosis. Fecundity of infertile women with minimal or mild endometriosis and women with unexplained infertility. Fertil Steril. 1998;69:1034–41.
42. Endometriosis and infertility: a committee opinion. Fertil Steril. 2012;98 (3):591–8.
43. Olive DL, Schwartz LB. Endometriosis. N Engl J Med. 1993;328:1759–69.
44. Cook AS, Rock JA. The role of laparoscopy in the treatment of endometriosis. Fertil Steril. 1995;55:663–80.
45. Guidice LC, Kao LC. Endometriosis. Lancet. 2004;364:1789–99.
46. Huang JY, Rosenwaks Z. In vitro fertilisation treatment and factors affecting success. Best Pract Res Clin Obstet Gynaecol. 2012;26(6):777–88.
47. Toya M, Saito H, Ohta N, et al. Moderate and severe endometriosis is associated with alterations in the cell cycle of granulosa cells in patients undergoing in vitro fertilization and embryo transfer. Fertil Steril. 2000;73:344–50.
48. Pellicer A, Oliveira N, Ruiz A, Remohi J, Simon C. Exploring the mechanism(s) of endometriosis-related infertilityan analysis of embryo development and implantation in assissted reproduction. Hum Reprod. 1995;10(2):91–97.
49. Harada T, Iwabe T, Terakawa N. Role of cytokines in endometriosis. Fertil Steril. 2001;76(1):1–10.
50. Tsudo T, Harada T, Iwabe T, Tanikawa M, Nagano Y, Ito M, et al. Altered gene expresion and secretion of interleukin-6 in stromal cells derived from endometriotic tissues. Fertil Steril. 2000;73:205–11.
51. Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohi J, Simon C. The follicular and endocrine environment in women with endometriosis: local and systemic cytokine production. Fertil Steril 1998;70:425–31.
52. Halme J., Becker S., Hammond MG, et al. Increased activation of pelvic macrophages in infertile women with mild endometriosis. Am J Obstet Gynecol. 1983;145:333–7.
53. Halme J, Becker S, Haskill S. Altered maturation and function macrophages. Thus cells with the appropriate receptors could of peritoneal macrophages: possible role in pathogenesis of endometriosis. Am J Obstet Gynecol. 1987;156:783–9.
54. McLaren J, Dealtry G, Prentice A, Charnock-Jones D, Smith S. Decreased levels of the potent regulator of monocyte/macrophage activation, interleukin-13, in the peritoneal fluid of patients with endometriosis. Hum Reprod. 1997;12(6):1307–10.
55. Fakih H, Marshall J. Subtle tubal abnormalities adversely affect gamete intrafallopian transfer outcome in women with endometriosis. Fertil Steril. 1994;62:799–801.
56. Guzick DS, Grefenstette I, Baffone K, et al. Infertility evaluation in infertile women: a model for answering the efficacy of infertility testing. Hum Reprod. 1994a;9:2306–10.
57. Nisolle M, Berlière M, Paindaveine B, Casanas-Roux F, Bourdon A, Donnez J. Histologic study of peritoneal endometriosis in infertile women. Fertil Steril. 1990;53:984–8.
58. Balasch J, Creus M, Fabregues F, Carmona F, Ordi J, Martinez-Roman S, et al. Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic paina prospective study. Hum Reprod. 1996;11:387–91.
59. Bérubé S, Marcoux S, Langevin S, Maheux R. Canadian collaborative group on endometriosis. Fecundity of infertile women with minimal or mild endometriosis and women with unexplained infertility. Fertil Steril. 1998;69:1034–1041.
60. Nakagawa K, Inoue M, Nishi Y, Sugiyama R, Motoyama K, Kuribayashi Y, Akira S, Sugiyama R. A new evaluation score that uses salpingoscopy to reflect fallopian tube function in infertile women. Fertil Steril. 2010;94(7):2753–57.
61. Jansen RP. Endocrine response in the Fallopian tube. Endocr Rev. 1984;5:525–51.
62. Karande VC, Pratt DE, Gleicher N. The assessment of tubal functional status by tubal perfusion pressure measurements. Hum Reprod. 1996;2:429–33.
63. Papaioannou S, Afnan M, Girling AJ, Cooarasamy A, McHugo JM, Sharif K. The potential value of tubal perfusion pressure measured during selective salpingography in predicting fertility. Hum Reprod. 2003;18:358–63.
64. Mol BWJ, Swant P, Bossuyt PMM, van Beurden M, van der Veen F. Reproducibility of the interpretation of hysterosalpingography in the diagnosis of tubal pathology. Hum Reprod. 1996;11:1204–08.
65. Glatstein IZ, Sleeper LA, Lavy Y, Simon A, Adoni A, Palti Z, Hurwitz A, Laufer N. Observer variability in the diagnosis and management of the hysterosalpingogram. Fertil Steril. 1997;67:233–7.
66. Mol BW, Collins JA, Burrows EA, van der Veen F, Bossuyt PM. Comparison of hysterosalpingography and laparoscopy in predicting infertility outcome. Hum Reprod. 1999;14:1237–42.
67. Tanahatoe S, Hompes PG, Lambalk CB. Accuracy of diagnostic laparoscopy in the infertility wash-ups before intrauterine insemination. Fertil Steril. 2003;79:361–6.
68. Karande V, Pratt D, Rabin DS, Gleicher N. The limited value of hysterosalpingography in answering tubal status and fertility potential. Fertil Steril. 1995a;63:1167–71.
69. Nakawaga K, Inoue M, Nishi Y, Sugiyama R, Motoyama K, Kuribayashi Y, Akira S, Sugiyama R. A new evaluation score that uses salpingoscopy to reflect fallopian tube function in infertile women. Fertil Steril. 2010;94(7):2753–57.
70. Arrestad G. Lunde 0, Moen M, Dalaker K. Infertility and chlamydial infection. Fertil Steril. 1987;58:787–90.
71. Akande VA, Hunt LP, Cahill DJ, Caul EO., Ford WC, Jenkins JM. Tubal damage in infertile women: prediction using chlamydia serology. Hum Reprod. 2003;18(9):1841–47.
72. Broeze KA, Opmeer BC, Coppus SFPJ., Van Geloven N, Alves MFC., Ånestad G, Bhattacharya S, Mol BW. Chlamydia antibody testing and diagnosing tubal pathology in subfertile women: an individual patient data meta-analysis. Hum Reprod Update. 2011;17(3):301–10.
73. Coppus SFPJ, Land JA, Opmeer BC, Teures P, Eijkemans MJC, Hompes PGA, Bossuyt PMM, van der Veen F, Mol BWJ, van der Steeg JW. Chlamydia trachomatis IgG seropositivity is associated with lower natural conception rates in ovulatory subfetile women without visible pathology. Hum Reprod. 2011;26(11):3061–7.
74. Bjercke, S., Purvis, K. Characteristics of women under fertility investigation with IgA/IgG seropositivity for Chlamydia trachomatis. European J Obstet Gynecol Reprod Biol. 1993;51(2):157–61.

75. Thomas K, Coughlin L, Mannion PT, Haddad NG. The value of Chlamydia trachomatis antibody testing as part of routine infertility investigations. Hum Reprod. 2000;15(5):1079–82.
76. Ruiz A, Guanes PP, Remohi J, Simon C, Minguez Y, Pellicer A. The role of in vitro fertilization and intracytoplasmic sperm injection in couples with unexplained infertility after failed intrauterine insemination. Fertil Steril. 1997;68:171–3.
77. Albougbar MA, Mansour RT, Serour GI, et al. Intracytoplasmatic sperm injection and conventional in vitro fertilization for sibling oocytes in cases of unexplained infertility and borderline semen. J Assist Reprod Genet. 1996;13:38–42.
78. Gurgan T, Urman B, Yarali H, Kisnisci HA. The results of in vitro fertilization-embryo transfer in couples with unexplained infertility failing to conceive with superovulation and intrauterine insemination. Fertil Steril. 1995;64:93.
79. Takeuchi S, Minoura H, Shibahara T, Shen X, Futamura N, Toyoda N. In vitro fertilization and intracytoplasmic sperm injection for couples with unexplained infertility after failed direct intraperitoneal insemination. J Assist Reprod Genet. 2000;17:515.
80. Munné S. Chromosome abnormalities and their relationship to morphology and development of human embryos. Reprod Biomed Online. 2006;12(2):234–53.
81. Munné S, Alikani M, Tomkin G, Grifo J, Cohen J. Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalities. Fertil Steril. 1995;64(2):382–91.
82. Gianaroli L, Magli MC, Munné S, Fiorentino A, Montanaro N, Ferraretti AP. Will preimplantation genetic diagnosis assist patients with a poor prognosis to achieve pregnancy? Hum Reprod. 1997;12:1762–7.
83. Pehlivan T, Rubio C, Rodrigo L, Romero J, Remohi J, Simón C, Pellicer A. Impact of preimplantation genetic diagnosis on IVF outcome in implantation failure patients. Reprod Biomed Online. 2003;6(2):232–7.
84. Stein A, Rufas O, Amit S, Avrech O, Pinkas H, Ovadia J, Fisch B. Assisted hatching by partial zona dissection of human pre-embryos in patients with recurrent implantation failure after in vitro fertilization. Fertil Steril. 1995;63(4):838–41.
85. Simón C, Mercader A, Garcia-Velasco J, Nikas G, Moreno C, Remohi J, Pellicer A. Coculture of human embryos with autologous human endometrial epithelial cells in patients with implantation failure. J Clin Endocrinol Metab. 1999;84(8):2638–46.
86. ShapiroBS, Richter KS, Harris DC, Daneshmand ST. Dramatic declines in implantation and pregnancy rates in patients who undergo repeated cycles of in vitro fertilization with blastocyst transfer after one or more failed attempts. Fertil Steril. 2001;76(3):538–42.
87. Tapia A, Gangi LM, Zegers-Hochschild F, Balmaceda J, Pommer R, Trejo L, Pacheco IM, Salvatierra AM, Henriquez S, Quezada M, Vargas M, Rios M, Munroe DJ, Croxatto HB, Velasquez L. Differences in the endometrial transcript profile during the receptive period between women who were refractory to implantation and those who achieved pregnancy. Hum Reprod. 2008; 23:340.
88. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Fertil Steril. 1950;1:3–25.
89. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Am J Obstet Gynecol. 1975;122:262–3.
90. Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril. 2004;82:1264–72.
91. Murray MJ, Meyer WR, Zaino RJ, Lessey BA, Novotny DB, Ireland K, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. Fertil Steril. 2004;81:1333–43.
92. Schena M, Shalon D, Davis RW, Brown PO. Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science. 1995; 270:467–70.
93. Díaz-Gimeno P, Horcajadas JA, Martínez-Conejero JA. A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. Fertil Steril. 2011;95(1):50–60.
94. Díaz-Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martínez-Conejero J, Alamá P, Garrido N, Pellicer A, Simón C. The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. Fertil Steril. 2013;99(2):508–17.
95. Horcajadas JA, Pellicer A, Simón C. Wide genomic analysis of human endometrial receptivity: new times, new opportunities. Hum Reprod Update. 2007;13(1):77–86.
96. Macklon NS, Geraedts JP, Fauser BC. Conception to ongoing pregnancy: the 'black box' of early pregnancy loss. Hum Reprod Update. 2002;8:333–43.
97. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. N Eng J Med. 1988;319:189–94.
98. Simon C, Landeras J, Zuzuarregui J, Martin J, Remohi J, Pellicer A. Early pregnancy losses in in vitro fertilization and oocyte donation. Fertil Steril. 1999;72:1061–5.
99. Troncoso C, Bosch E, Rubio C, Remohí J, Simón C, Pellicer A. The origin of biochemical pregnancies: lessons learned from preimplantation genetic diagnosis. Fertil Steril. 2003;79(2):449–50.
100. Kunz G, Beil D, Deiniger H, Einspanier A, Mall G, Leyendecker G. The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract. Adv Exp Med Biol. 1997;424:267–77.
101. Kunz G, Beil D, Deininger H, Wildt L, Leyendecker G. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. Hum Reprod. 1996;11(3):627–32.
102. Leyendecker G, Kunz G, Wildt L, Beil D, Deininger H. Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. Hum Reprod. 1996;11(7):1542–51.
103. Kissler S, Zangos S, Wiegratz I, Kohl J, Rody A, Gaetje R, Doebert N, Wildt L, Kunz G, Leyendecker G, Kaufmann M. Uterotubal sperm transport and its impairment in endometriosis and adenomyosis. Ann N Y Acad Sci. 2007;1101:38–48.
104. Kissler S, Hamscho N, Zangos S, Gätje R, Müller A, Rody A, Döbert N, Menzel C, Grünwald F, Siebzehnrübl E, et al. Diminished pregnancy rates in endometriosis due to impaired uterotubal transport assessed by hysterosalpingoscintigraphy. BJOG. 2005;112(10):1391–6.
105. Kissler S, Wildt L, Schmiedehausen K, et al. Predictive value of impaired uterine transport function assessed by negative hysterosalpingoscintigraphy (HSSG). Eur J Obstet Gynecol Reprod Biol. 2004;113:204–208.