Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/17196
DOI URL: http://dx.doi.org/10.21474/IJAR01/17196

RESEARCH ARTICLE

ULTRASOUND IN THE ETIOLOGICAL ASSESSMENT OF EMBRYONIC IMPLANTATION FAILURES AT THE FERTILIA MEDICAL CLINIC IN BAMAKO

Mamadou Dembélé[1,3], Alassane Kouma[1], Ilias Guindo[1], Souleymane Sanogo[1], Zoumana Cheick Berete[2], Mamadou N'Diaye[1], Brahima Doumbia[1], Oncoumba Diarra[1], Ousmane Traoré[1], Issa Cissé[1], Aboubacar Sidiki N'Diaye[1], Bandiougou Doucouré[3], Youssouf Yalcouyé[3], Adama Diaman Keita[1] and Siaka Sidibe[1]

1. Faculty of Medicine and Odonto-Stomatology of Bamako (FMOS), Bamako, Mali.
2. Department of Education and Research in Public Health (DERSP), Bamako, Mali.
3. Fertilia Medical Clinic.

Manuscript Info

Manuscript History
Received: 26 April 2023
Final Accepted: 31 May 2023
Published: June 2023

Key words:-
Ultrasound, Repeated Embryo Implantation Failure / In Vitro Fertilization

Abstract

Recurrent implantation failure refers to failure to achieve a clinical pregnancy after the transfer of at least four embryos in at least three fresh or frozen cycles in a woman under 40 years of age. Implantation failure can be a consequence of embryonic or uterine factors. Thorough investigations must be necessary to determine whether there is an embryonic or uterine cause. Various uterine pathologies, including fibroids, endometrial lesions, polyps, congenital anomalies and intrauterine adhesions, vascular parameters should be explored by ultrasound to aid in the diagnosis of the causes of embryo implantation failures [1].

Aims:

- To describe the sonographic lesions likely to explain embryo implantation failures.
- To determine the correlation between ultrasound lesions detected during our study and embryo implantation failures.

Subjects And Methods: This was a cross-sectional, descriptive study concerning 165 women collected between January 2016 and January 2022 at the Fertilia medical clinic in Bamako. The study population consisted of consenting women in whom at least three unsuccessful attempts to transfer good quality fresh or frozen embryos were made. All of our patients underwent a biological assessment, but our study focused on the contribution of ultrasound. Ultrasounds were performed by endocavitary and suprapubic route with General Electric Voluson E8, Vivid 3 and Logic9 devices.

Results: 165 women were recruited into our. The average age was 38 years with extremes ranging from 23 to 52 years. 86 patients or 52% were between 30 and 40 years old. 94 patients or 57% had made at least three unsuccessful attempts to transfer good quality embryos. 139 patients or 84.24% had at least one ultrasound anomaly. The most common pathologies were adenomyosis (30.3%), endometritis (13.94%), hydrosalpinx (4.24%), a high pulsatility index (12.12%), the presence of notch in one or both uterine arteries (7.27 %),

Corresponding Author:- Mamadou Dembélé
Address:- Faculty of Medicine and Odonto-Stomatology of Bamako (FMOS), Bamako, Mali.

polymyomatous uterus (26%), congenital malformation (1.21%), polyp (4.85%).

Conclusion: Repeated embryo implantation failures are partly due to the embryo and partly to the uterus or its annexes. Ultrasound is a tool of choice in developing countries such as ours to diagnose the causes of these implantation failures and to allow infertile couples to procreate. We were able to highlight the relationships that exist between abnormalities detected on ultrasound and repeated embryo implantation failures.

……

Introduction:-

Infertility affects between 8 and 12% of couples of childbearing age worldwide [1]. One of the solutions for infertile couples to try to overcome infertility is to resort to medically assisted procreation (MAP). ART includes the techniques of intrauterine insemination (IUI) and conventional in vitro fertilization (IVF) (IVFc) or with sperm microinjection (ICSI). Despite improvements in assisted reproduction techniques over the past few decades, the results remain limited, with around one out of nine IUI attempts and less than one out of six IVF attempts resulting in a live birth [2]. One of the major causes of these limited results remains implantation failure, which clinically corresponds to the absence of embryonic implantation or to biochemical pregnancy [3]. Implantation failures can have multiple causes: an embryonic cause, an endometrial cause, or simply result from a lack of synchronization between the developing blastocyst and the receptive endometrium [4, 6]. Indeed, embryo implantation requires coordinated bidirectional communication between the embryo and the endometrium. The endometrium is receptive during a short period of the menstrual cycle: the "implantation window" which theoretically extends between days 20 (d20) and 24 (d24) of a menstrual cycle of 28 days, i.e. between 7 and 11 days after the luteinizing hormone (LH) peak (LH+7 and LH+11, respectively) [7, 9]. Stromal endometrial cells, which initially presented a phenotype of elongated epithelial cells at the beginning of the luteal phase, then transform into secretory deciduous cells of rounded morphology under the action of progesterone [10]. In parallel, the proliferation and differentiation of endometrial epithelial cells lead to the development of secretory glands in the endometrium [10].Implantation takes place in three successive phases: apposition, adhesion and invasion [11]. During the apposition stage, the embryonic pole of the hatched blastocyst orients itself facing the maternal endometrium and begins to express adhesion molecules on its surface (including L-selectins and certain integrins) [11]. In parallel, pinopods (transient membrane micro-protrusions) develop at the apical pole of endometrial epithelial cells under the action of progesterone [12,13]. These pinopods could facilitate the attraction of the blastocyst towards the endometrium as well as promote its survival via the release of secretory vesicles containing nutrients [12]. Pinopods also express L-selectin ligands, which interact with L-selectins expressed by the blastocyst during the apposition and adhesion stages, thus promoting the establishment of close contact between the blastocyst and the endometrium. During the adhesion stage, the blastocyst attaches more stably to the uterine epithelium through the cleavage of mucin-1 (MUC-1, an anti-adhesion molecule) and through certain integrins (eg, aVb3) expressed on the surface of endometrial epithelial cells [11]. During the invasion stage, the trophoblast expresses protrusions (called invadopodia) which interfere through the epithelial cells and participate in the degradation of the extracellular matrix. Macrophages, lymphocytes and leukocytes (in particular activated uterine natural killers (uNK)) participate in the control of trophoblastic invasion, immunological tolerance, vascular remodeling, as well as the maintenance of decidualisation during the stage of invasion. The trophoblast then differentiates into cytotrophoblast and syncitiotrophoblast, leading to the complete burial of the blastocyst in the endometrium around LH + 9 [11]. To date, the understanding of the physiological and pathological mechanisms involved in human embryo implantation is still far from complete. Implantation failures are frequent in spontaneous fertility as in ART. Indeed, less than a third of conceptions seem to result in a birth in spontaneous fertility, with 30% of fertilized oocytes failing to implant and 30% of implanted embryos stopping their development before the fourth week of amenorrhea [5].These results seem comparable to those currently obtained in ART. To date, the understanding of the causes involved in these implantation failures is progressing, in particular thanks to studies carried out in patients subject to repeated implantation failures. Embryonic aneuploidy and mosaicism are found in a significant proportion of these failures [14, 15]. Nevertheless, other embryonic or endometrial factors are also involved, in particular, in the 30 to 50% of attempts associated with the transfer of evolving euploid blastocyst(s) which nevertheless result in an absence of clinical pregnancy. [16,17]. Failures caused by the absence or time lag of the implantation window could benefit from the current development of innovative approaches to the evaluation of endometrial receptivity, thus optimizing the conditions for carrying out

embryo transfer and favoring the increase in rates. of success in ART. Any cause tending to affect a stage of the complex process described above will be considered as a failure factor. In this study we focused more on uterine ultrasound factors. The objective of this study was to summarize the ultrasound causes that could explain the asynchrony between the embryo and the endometrium, something that will lead to implantation failure.

Materials And Method:-

This was a cross-sectional, descriptive study concerning 165 women collected between January 2016 and January 2022 at the Fertilia medical clinic in Bamako. The study population consisted of consenting women in whom at least three unsuccessful attempts to transfer good quality fresh or frozen embryos were made. All of our patients underwent a biological assessment, but our study focused on the contribution of ultrasound.

Exploration Techniques:

Ultrasounds were performed by endocavitary and suprapubic route with General Electric Voluson E8, Vivid 3 and Logic9 devices, all equipped with Doppler.

Data Processing And Analysis:

The data collected on the technical sheets were entered and analyzed using SPSS software. Spearman's and Pearson's correlation tests were used to determine the degree of significance during comparisons at the 5% level.

Results:-

165 women were recruited into our study. The average age was 38 years with extremes ranging from 23 to 52 years. 86 patients or 52% were between 30 and 40 years old. 94 patients or 57% had made at least three unsuccessful attempts to transfer good quality embryos. 139 patients or 84.24% had at least one ultrasound anomaly. The most common pathologies were adenomyosis (30.3%), endometritis (13.94%), hydrosalpinx (4.24%), a high pulsatility index (12.12%), the presence of notch of one or both uterine arteries (7.27 %), polymyomatous uterus (26%), congenital malformation (1.21%), polyp (4.85%).

Table I:- Distribution Of Patients According To Echographic Abnormalities

Adenomyosis was the most encountered anomaly with 30.3% followed by myoma(s) and chronic endometritis which was an anatomopathological diagnosis. The correlation between adenomyosis and repeated embryo implantation failure was significant ($p<0.005$); for myomatous uterus $p=0.003$ and for chronic endometritis $p<0.005$.

ECHOGRAPHIC ABNORMALITY	NUMBER	PERCENTAGE (%)
CHRONIC ENDOMETRITIS (ANATOMOPATHOL)	23	13.94
ADENOMYOSIS	**50**	**30.3**
MYOMA(S)	43	26
ENDOMETRIAL POLYP	8	4.85
HYDROSALPINX	7	4.24
PULSATILITY INDEX ≥3	20	12.12
NOTCH	12	7.27
UTERINE MALFORMATION	2	1.21
TOTAL=	**165**	**100%**

Discussion:-

Maternal Age:

Our study focused on a sample of 165 women among whom the average age was 38 years with extremes ranging from 23 to 52 years. Maternal age is an important factor to take into account because for many authors a maternal age above 40 years is deleterious for embryo implantation. Age is the most important predictor of success in ART. Indeed, even if the embryos have morphological characteristics of normal development, at the same stage, studies show aneuploidy rates of 33% and more after 40 years [18]. Thus, according to the study by Luke et al (2012), the cumulative live birth rate decreased significantly with the age of the patient and the rank of her attempt. With, in particular, in patients aged 41-42 years, a cumulative birth rate of 18.6% after the 3rd attempt, whereas it is 63.3% in patients under 31 years old [19]. It therefore seems important to consider only patients under 40 years of age in order to be able to affirm the transfer of embryos of good morphological quality and with an aneuploidy rate that is a priori acceptable.

Ultrasound Abnormalities:

Adenomyosis:

Also called internal endometriosis was the most represented ultrasound anomaly with 30.3%. There is literature evidence available to suggest that adenomyosis has an adverse effect on female fertility (Maheshwari et al., 2012 [20]; Sunkara and Khan, 2012 [21]). In addition Younes et al. [22] found in a recent meta-analysis that adenomyosis was responsible for implant failure in 66% of cases.

Fibroids:

Our study recorded 26% of fibroid cases and most of them were submucosal fibroids. Submucosal fibroids are clearly associated with reduced implantation rates [23, 24, 25], the role of intramural fibroids (FIGO classification 3 and 4) is much more controversial in implantation failures [26]. The size of the intramural fibroids as well as its relationship with the uterine cavity could be decisive parameters with, for example, altered implantation rates only in the case of an intramural fibroid of more than 4 cm [23, 27, 28].

Chronic Endometritis:

It is an infectious and inflammatory pathology of the endometrium, asymptomatic (unlike acute endometritis), which is characterized by a plasma cell infiltrate within the endometrial stroma on pathology. In our study, it represented nearly 14% of cases. This score is very close to that of Johnston-Mac Ananny et al. [29] and Cicinelli E. et al. [30] who found respectively 15.5% and 17% of cases of chronic endometritis in women undergoing ART with successive implantation failures. The presence of this inflammation is very harmful for implantation $p<0.005$.

High Pulsatility Index (PI):

We found 12.12% of cases where the pulsatility index was ≥3. The higher the PI, the greater the downstream arterial resistance and the poorer the uterine perfusion and consequently the endometrial perfusion is affected, thus the chances of implantation decrease. Ardaens et al. [31] and Steer CV. et al. [32] reported in their series that high PI is detrimental to implantation.

The Notch:

It is a protodiastolic notch, a notch appearing on the plot of the recording of the uterine blood flow. Its presence is pejorative for the implantation and the rest of the pregnancy. Our study showed just over 7% of Notch cases. Ardaens Y. et al [33] reported an 83% pregnancy rate without notch, just as Maurice N. Cauchi et al [34] found a low pregnancy rate with the presence of notch. In our study, no link was found between the presence of the notch and implantation failure ($p=1.00$).

Endometrial Polyp:

The effect of endometrial polyps is poorly understood and their impact on implantation is controversial. We reported in our study note less than 5% of cases. Perez M.T. et al. report that if their size reaches 1.5 cm they can disrupt implantation [35]. Isikoglu M. et al. [36] found that polyps larger than 1.5cm are responsible for implantation failure in 33% of cases.

Hydrosalpinx:

It is one of the factors that deteriorate the quality of the endometrium and therefore affect implantation. We found just over 4% of cases of hydrosalpinx in our patients. Camus, E. et al. [37] found that hydrosalpinx was responsible for repeated abortions and implantation failures in 35% of cases in 1999.

Uterine malformations:

They were rare in our study, 1.21%. They were bicornuate wombs. A study published in 1996 by Lavergne et al. [38] shows that ART implantation rates are significantly lower in patients with uterine malformation and found 6% of cases and the difference was significant with $p<0.005$.

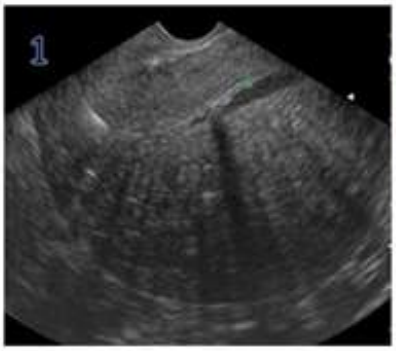
Conclusion:-

The repeated failures of embryo implantation are partly due to the embryo and partly to the uterus or its annexes. Ultrasound is a tool of choice in developing countries such as ours to diagnose the causes of these implantation failures and to allow infertile couples to procreate. We were able to highlight the relationships that exist between the abnormalities detected on ultrasound and the repeated failures of embryo implantation and also to highlight the maternal age which beyond 40 years alters the embryonic quality and reduces the chances of implantation.

Declaration of conflict of interest:
All authors declared having no conflict of interest.

Iconography

FIG1: ADENOMYOTIC UTERUS



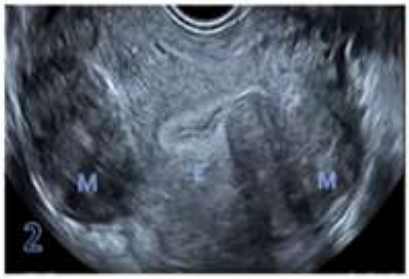


FIG2: UTERUS: E= ENDOMETER, M= MYOMA

FIG3: LARGE LEFT OBSTRUCTIVE HYDROSALPINX

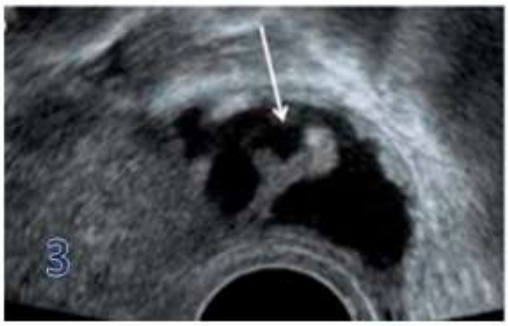


FIG3: Transvaginal ultrasound of a 32-year-old infertile woman with amenorrhea, revealing (A) a hyperechoic endométrial band (Arrow); (B) A color-coded Doppler scan showing flicker artifact (arrow), consistent with the presence of osteoid metaplasia

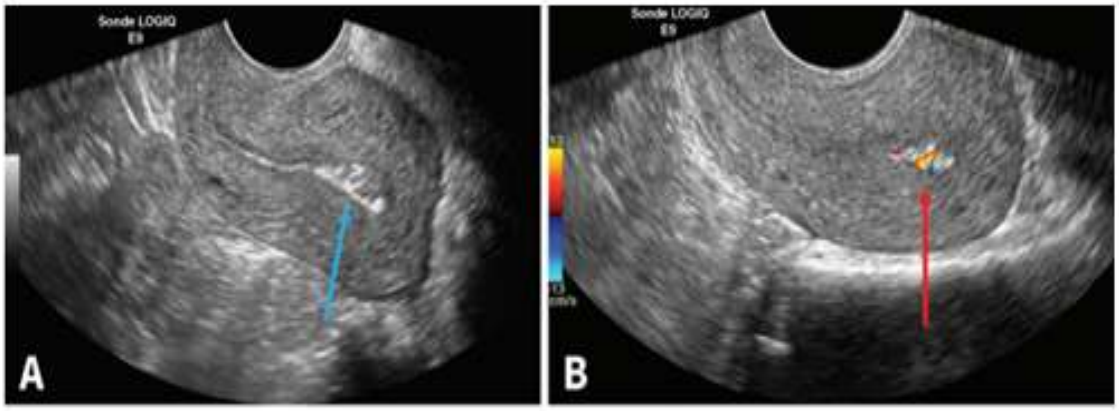
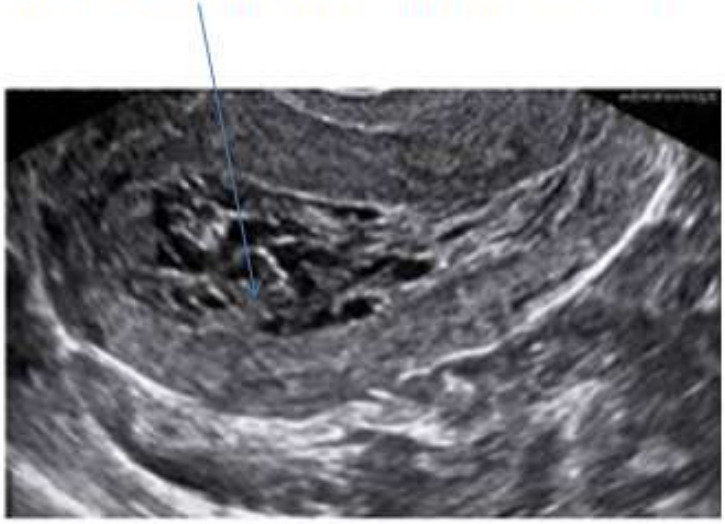


FIG5: UTERUS LONGITUDINAL SECTION: BULKY GLANDULOCYSTIC ENDOMETRIAL POLYP



Bibliographic References:-

1- Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update 2015;21(4):411–26.
2- Medical and scientific report 2017 – AMP [Internet]; 2020 [cited 2020 Jan 31]. Availableat: https://rams.agence-biomedecine.fr/assistance-medicale-la-procreation.
3- Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, et al. Recurrent implantation failure: definition and management. Reprod Biomed Online 2014;28(1):14–38.
4- Messaoudi S, El Kasmi I, Bourdiec A, Crespo K, Bissonnette L, Le Saint C, et al. 15 years of transcriptomic analysis on endometrial receptivity: what have we learned? Fertil Res Pract2019;5:9.
5- Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. BMC Med 2013;11:154.
6- Valdes CT, Schutt A, Simon C. Implantation failure of endometrial origin: it is not pathology, but our failure to synchronize the developing embryo with a receptive endometrium. FertilSteril 2017;108(1):15–8.
7- Lessey BA. Assessment of endometrial receptivity. FertilSteril 2011;96(3):522–9.
8- Paulson RJ. Hormonal induction of endometrial receptivity. FertilSteril 2011;96(3):530–5.
9- Kresowik JDK, Devor EJ, Van Voorhis BJ, Leslie KK. MicroRNA-31 is significantly elevated in both human endometrium and serum during the window of implantation: a potential biomarker for optimum receptivity. Biol Reprod 2014;91(1):17.
10- Sar-Shalom Nahshon C, Sagi-Dain L, Wiener-Megnazi Z, Dirnfeld M. The impact of intentional endometrial injury on reproductive outcomes: a systematic review and meta-analysis. Hum Reprod Update 2019;25(1):95–113.
11- Ochoa-Bernal MA, Fazleabas AT. Physiologic events of embryo implantation and decidualization in human and non-human primates. Int J Mol Sci 2020;21(6):1973.
12- Rarani FZ, Borhani F, Rashidi B. Endometrial pinopod biomarkers: molecules and microRNAs. J Cell Physiol 2018;233(12):9145–58.
13- Jin XY, Zhao LJ, Luo DH, Liu L, Dai YD, Hu XX, et al. Pinopod score around the time of implantation is predictive of successful implantation following frozen embryo transfer in hormone replacement cycles. Hum ReprodOxf Engl 2017;32(12):2394–403.
14- Victor AR, Tyndall JC, Brake AJ, Lepkowsky LT, Murphy AE, Griffin DK, et al. One hundred mosaic embryos transferred prospectively in a single clinic: exploring when and why they result in healthy pregnancies. FertilSteril 2019;111(2):280–93.
15- Munne´ S, Spinella F, Grifo J, Zhang J, Beltran MP, Fragouli E, et al. Clinical outcomes after the transfer of blastocysts characterized as mosaic by high resolution next generation sequencing – further insights. Eur J Med Genet 2020;63(2):103741.

16- Munne´ S, Kaplan B, Frattarelli JL, Child T, Nakhuda G, Shamma FN, et al. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. FertilSteril 2019;112(6) [1071–1079.e7].
17- Wang A, Lathi R, Kort J, Westphal L. Anti-Mu¨ llerian hormone in association with euploid embryo transfer outcomes. Reprod Biomed Online 2019;39(4):609–16.
18- Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, et al. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. Fertil Sterile. 2014 Mar;101(3):656-663.e1.
19- Luke B, Brown MB, Wantman E, Lederman A, Gibbons W, Schattman GL, et al. Cumulative Birth Rates with Linked Assisted Reproductive Technology Cycles. N Engl J Med. 2012 Jun 28;366(26):2483-91
20- Maheshwari, A., Gurunath, S., Fatima, F., Bhattacharya, S., 2012. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. Hmm. Repr. Update 18, 374–392
21- Sunkara, S.K., Khan, K.S., 2012. Adenomyosis and female fertility: a critical review of the evidence. J. Obstet. Gynecol. 32, 113–116.
22- Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fertil Sterile. 2017;108(3):483-490.e3
23- Klatsky PC, Lane DE, Ryan IP, Fujimoto VY. The effect of fibroids without cavity involvement on ART outcomes independent of ovarian age. Hum Repr. 2007 Feb;22(2):5216. 88.
24- Eldar-Geva T, Meagher S, Healy DL, MacLachlan V, Breheny S, Wood C. Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. Fertil Sterile. 1998 Oct;70(4):687-91.
25- Casini ML, Rossi F, Agostini R, Unfer V. Effects of the position of fibroids on fertility. Gynecolendocrinol. 2006 Feb;22(2):106-9.
26- Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Repr. 2010 Feb;25(2):418-29.98
27- Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. Am J Obstet Gynecol. Apr 2008; 198(4): 357-66.
28- Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Melo NR, Abdelmassih R. Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization-intracytoplasmic sperm injection. Fertil Sterile. 2004 Mar;81(3):582-7.
29- Johnston-Mac Ananny EB, Hartnett J, Engmann LL, Nulsen JC, Sanders MM, Benadiva CA. Chronic endometritis is a frequent finding in women with recurrent implantation failure after in vitro fertilization. Fertility and Sterility. 2010 Jan 15;93(2):437-41.
30- Cicinelli E, Matteo M, Tinelli R, Lepera A, Alfonso R, Indraccolo U, et al. Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. Hum Repr. 2015 Feb 1;30(2):323-30.
31- Ardaens et al. Ultrasound and pelvic imaging in gynecological practice; chapters 2 and 5. In.
32- Steer CV, Campbell S, Pampiglione JS, Kingsland CR, Mason BA, Collins WP. Transvaginal color flow imaging of the uterine arteries during the ovarian and menstrual cycles. Hum Repr. 1990 May 1;5(4):391-5.
33- Ardaens Y. Imaging and couple infertility, book, 336p, 1998
34- Maurice N. Cauchi et al. Predictive Factors in Recurrent Spontaneous Aborters- A Multicenter Study, 1995.
35- Pérez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, et al. Endometrial polyps and their involvement in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. Hum Repr. 2005 Jun 1;20(6):1632-5.
36- Isikoglu M, Berkkanoglu M, Senturk Z, Coetzee K, Ozgur K. Endometrial polyps smaller than 1.5 cm do not affect ICSI outcome. Reproductive BioMedicine Online. 2021 Feb 08;12(2):199-204.
37- Camus, E., Poncelet, C., Goffinet, F., Wainer, B., Merlet, F., Nisand, I., Philippe, H.J., 1999. Pregnancy rates after in-vitrofertilization in cases of tubal infertility with and without hydrosalpinx: a meta-analysis of published comparative studies. Hmm. Repr. 14, 1243–1249.
38- Lavergne N, Aristizabal J, Zarka V, Erny R, Hedon B. Uterine anomalies and in vitro fertilization: what are the results? Eur J ObstetGynecolReprod Biol. 1996 Sep;68(12):29-34.