Does different subfertility etiology affect pregnancy rates in intrauterine insemination cycles?

Batuhan TURGAY*, Yavuz Emre ŞÜKÜR, Batuhan ÖZMEN, Rusen AYTAÇ, Cem Somer ATABEKOĞLU, Bülent BERKER, Murat SÖNMEZER
Department of Obstetrics and Gynecology, School of Medicine, Ankara University, Ankara, Turkey

1. Introduction
Subfertility is defined as the failure to conceive after 1 year of regular, unprotected intercourse. It affects approximately 8%–15% of couples [1]. Intrauterine insemination (IUI) is a procedure in which processed and concentrated motile sperm are placed directly into the uterine cavity with an insemination canula. Intrauterine insemination, with or without ovarian stimulation, is frequently used as a first-line infertility treatment because it is a relatively inexpensive, less invasive, and effective method which is indicated for different subfertility etiologies [2–4]. Mild male subfertility, minimal–mild endometriosis, unexplained subfertility, and several physical–psychosexual problems are major indications for IUI [5].

The intrauterine insemination procedure can be applied with normal menstrual cycles or controlled ovarian stimulation (COS). Clomiphene citrate, letrozole, or gonadotropins can be used for COS. Furthermore, it is reported that the best pregnancy rate is achieved by COS–IUI using gonadotropins when compared to other treatments [6–8].

The live birth rate with the IUI procedure has been reported as between 8.5% and 12.2% in different studies [9]. There is sufficient evidence that COS–IUI improves pregnancy rates in unexplained subfertility and minimal–mild endometriosis, but its value for mild male factor subfertility is still debated [4,10–14]. The aim of the present study was to compare live birth rates after COS–IUI in subfertile patients with male infertility, minimal–mild endometriosis, and unexplained subfertility groups.

1. Background/aim:
To investigate the relationship between subfertility etiologies and success rates in controlled ovarian stimulation and intrauterine insemination (COS–IUI) cycles.

2. Materials and methods:
The medical records of 218 couples who applied to a university-based fertility center were analyzed retrospectively. Detailed infertility examination data and pregnancy outcomes were compared according to different subfertility etiologies. The study groups with regard to subfertility etiologies were minimal–mild endometriosis, unexplained infertility, and mild male infertility. The primary outcome measure was live birth rate.

Results:
There were no statistically significant differences between the groups regarding demographics except for total motile sperm count. Live birth rates in the male infertility group were comparable to the endometriosis and unexplained infertility groups (6.6%, 11.9%, and 10.3%, respectively; P = 0.63).

Conclusion:
The success rate of the mild male subfertility group following COS–IUI cycles for live birth rates was similar to those of the endometriosis and unexplained subfertility groups.

Key words: Intrauterine insemination, assisted reproductive technology, fertility etiology

Received: 22.02.2019
Accepted/Published Online: 22.07.2019
Final Version: 24.10.2019
Continuous variables were compared with a one-way ANOVA test. Categorical variables were compared with a chi-square test. A P value of <0.05 was considered statistically significant.

3. Results
In total, 218 couples were included in this study. There were 42 (19.2%) couples in the endometriosis group, 116 (53.2%) couples in the unexplained infertility group, and 60 (27.6%) couples in the male infertility group. Basic demographic characteristics are presented in Table 1. The groups had similar demographic characteristics. The mean time interval between laparoscopic surgery and IUI was 2.1 ± 1.7 months in the endometriosis group. The mean TMSC of the mild male infertility group was 12.1 × 10^6, which was significantly lower than for the other groups (P < 0.001).

The live birth rate of the entire study population was 9.6%. The live birth rates were 11.9%, 10.3%, and 6.6%, respectively, in the endometriosis, unexplained infertility, and mild male infertility groups (P = 0.63). In addition, there were no statistically significant differences between the groups for biochemical pregnancy and miscarriage rates (Table 2).

4. Discussion
In this study, we compared live birth rates between subfertile couples with mild male infertility, minimal–mild endometriosis, and unexplained infertility, and observed that live birth rates were similar between the groups.

Controlled ovarian stimulation and IUI increases pregnancy rates in subfertile women regardless of infertility etiology; IUI without ovarian stimulation has no effect on live birth rates [18–22]. However, previous studies did not compare the pregnancy rates between different subfertility groups. A recent study from Brazil which included 237 IUI cycles in 198 patients concluded that infertility etiology did not affect pregnancy rates [23]. Although their results seem similar to ours, the primary outcome of that study was clinical pregnancy rate, not live birth rate. This was the greatest limitation of that study.

Intruterine insemination is a frequently used treatment option for subfertile couples. In our study, live birth rates were 10.3% and 11.9% in the unexplained infertility and endometriosis groups, respectively. Werbrouck et al. reported that pregnancy rates were similar between unexplained infertility and minimal–mild endometriosis groups (AFS stage I/II) within 6 months after surgical treatment [24]. Prado-Perez et al. also found no statistically significant differences in pregnancy rates of couples with unexplained infertility and stage I or II endometriosis who underwent IUI treatment [25]. The results of our study were in accordance with those of the aforementioned studies which showed similar live birth rates between unexplained infertility and minimal–mild endometriosis.
Although there was no statistically significant difference in live birth rate between different subfertility groups, it is important to note that the highest live birth rate was found in the endometriosis group (11.9%). Several studies have suggested lower pregnancy rates in couples with endometriosis than others following IUI [26,27]. However, we failed to demonstrate such a result. This might be as a result of the low number of subjects, as well as surgical treatment of endometriosis by laparoscopy. The benefits of laparoscopic surgery on pregnancy rates were also demonstrated in a previous Cochrane review [28].

In our study, complete laparoscopic surgical removal was performed in the endometriosis group before COS–IUI treatment, which could have increased the live birth rate. Miller et al. reported a 12.4% pregnancy rate per cycle when the TMSC was over 20 million, and 7.4% when the TMSC was between 10 and 20 million [29]. In our study, we found that the biochemical pregnancy rate was 15% and the live birth rate was 6.6% when mean TMSC was 11.6 million, which was in accordance with the abovementioned study. In the mild male infertility group, the miscarriage rate was the highest of all of the groups. We could not analyze any data other than motility with a spermiogram. The high miscarriage rate in the mild male infertility group could be related to sperm morphology, but we cannot comment further about the effect of the spermiogram because of the limitations of the retrospective study. On the other hand, a recent study which included 501 couples stated that abnormal sperm morphology did not impact live birth rates [30].

Success of IUI treatment is still a debate of importance for subfertile couples. The most recent NICE 2013 guidelines advised against offering routine IUI for people with unexplained infertility, mild endometriosis, or mild male factor infertility who are having regular unprotected sexual intercourse. According to the NICE guidelines, IVF should be considered after 2 years of unsuccessful conception. On the contrary, a recent review from 2017 suggested that IUI procedure should be undergone at least 3 cycles prior to in vitro fertilization (IVF) in couples with

---

**Table 1.** Demographic characteristics of subfertility groups.

|                      | Endometriosis (n = 42) | Unexplained (n = 116) | Mild Male (n = 60) | P-value |
|----------------------|------------------------|-----------------------|--------------------|---------|
| Age, years           | 2 ± 9.1 ± 5.1          | 28.4 ± 4.3            | 29.2 ± 4.8         | 0.48    |
| Duration of infertility, years | 3.8 ± 1.9            | 3.6 ± 2.1             | 4.1 ± 2.5          | 0.35    |
| Previous IUI, n (%)  | 2 (4.7)                | 7 (5.1)               | 4 (6.6)            | 0.92    |
| Unilateral tubal blockage, n (%) | 4 (9.5)                | 10 (8.6)              | 7 (11.6)           | 0.81    |
| Mean antral follicle count | 9.2 ± 1.1            | 9.1 ± 0.9             | 8.9 ± 0.7          | 0.20    |
| Baseline FSH, IU/mL  | 7.9 ± 2.3              | 7.4 ± 3.1             | 7.7 ± 2.8          | 0.58    |
| E2 (pg/mL)           | 40.2 ± 19.2            | 48.3 ± 18.3           | 46.8 ± 20.2        | 0.06    |
| PRL (ng/mL)          | 18 ± 7.1               | 15.2 ± 7.2            | 17.2 ± 8.9         | 0.07    |
| TSH (mIU/L)          | 2.1 ± 0.8              | 2.2 ± 0.9             | 1.9 ± 0.9          | 0.29    |
| Total gonadotropin dose (IU) | 970.4 ± 180.2        | 980.3 ± 170.3         | 930.4 ± 200.4      | 0.21    |
| Duration of stimulation (days) | 12.8 ± 3.9           | 11.0 ± 4.4            | 11.8 ± 4.3         | 0.60    |
| TMSC (×10⁹)          | 47.9 ± 7.2             | 44.3 ± 8.2            | 12.1 ± 4.1         | <0.001  |

Note: The values are presented as mean. AFC: Atrial follicular count; TMSC: total motile sperm count.

**Table 2.** The pregnancy outcome among subfertility groups.

|                      | Endometriosis group (n = 42) | Unexplained group (n = 116) | Mild male group (n = 60) | P |
|----------------------|-----------------------------|-----------------------------|------------------------|---|
| Biochemical pregnancy (%) | 7 (16.6)                    | 15 (12.9)                   | 9 (15)                 | 0.82 |
| Live birth (%)        | 5 (11.9)                    | 12 (10.3)                   | 4 (6.6)                | 0.63 |
| Miscarriage, 2(%)     | 2 (4.7)                     | 3 (2.6)                     | 5 (8.4)                | 0.22 |

---

2 National Institute for Health and Clinical Excellence (NICE) guidelines. 2013 Feb.https://www.nice.org.uk/guidance/cg156/ifp/chapter/intrauterine-insemination.
unexplained infertility and for men with a TMSC of >10 million [31]. No suggestion was presented for patients with mild endometriosis in that paper. According to the recent Cochrane review concerning male subfertility, there is no evidence of a difference in live birth rates between COS–IUI and timed intercourse [14]. They reported that this result was very low-quality evidence. On the other hand, we found similar pregnancy rates between the study groups. Although we did not compare live birth rates between subfertility etiology and timed intercourse, our results, especially in the male subfertility group, are valuable. We suggest COS–IUI treatment should be considered in couples with male subfertility before IVF procedures because of its substantial live birth rate, its simplicity, and low cost.

The main strengths of the present study were using live birth rate as the primary outcome measure and evaluating only the first COS–IUI cycle of each couple to prevent crossover bias. The major limitations of our study were the retrospective design and the low number of subjects, particularly in the endometriosis group. However, we could not include more subjects in such a study using strict inclusion and exclusion criteria conducted in a single center. Another limitation of the study was the lack of a hypothetical power analysis.

In conclusion, different subfertility etiologies do not affect the success of COS–IUI treatment in terms of live birth rate. The success rate of mild male subfertility following a COS–IUI cycle for live birth rates is similar to those of the endometriosis and unexplained subfertility groups. Further large prospective studies are needed to determine the exact effect of subfertility etiology on the success of COS–IUI treatment.

References

1. Stephen EH, Chandra A. Declining estimates of infertility in the United States: 1982–2002. Fertility and Sterility 2006; 86(3): 516-323. doi: 10.1016/j.fertnstert.2006.02.129

2. Dickey RP, Pyrzak R, Lu PY, Taylor SN, Rye PH. Comparison of the sperm quality necessary for successful intrauterine insemination with World Health Organization threshold values for normal sperm. Fertility and Sterility 1999; 71(4): 684-689. doi: 10.1016/s0015-0282(98)00519-6

3. Kennedy S, Bergqvist A, Chapron C, D’Hooghe T, Dunselman G et al. ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group. ESHRE guidelines for the diagnosis and treatment of endometriosis. Human Reproduction 2005; 20(10): 2698-2704. doi: 10.1093/humrep/dei135

4. Practice Committee of the American Society for Reproductive Medicine. Effectiveness and treatment for unexplained infertility. Fertility and Sterility 2006; 86(Suppl 1): S111-S114. doi: 10.1016/j.fertnstert.2006.07.1475

5. Francavilla F, Sciarretta F, Sorgentone S, Necozione S, Santucci R et al. Intrauterine insemination with or without mild ovarian stimulation in couples with male subfertility due to oligo/ astheno- and/or teratozoospermia or antisperm antibodies: a prospective cross-over trial. Fertility and Sterility 2009; 92(3): 1009-1011. doi: 10.1016/j.fertnstert.2009.01.112

6. Hull MG. Effectiveness of infertility treatments: choice and comparative analysis. International Journal of Gynecology and Obstetrics 1994; 47(2): 99-108. doi: 10.1016/0020-7292(94)90348-4

7. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD et al. Letrozole, gonadotropin, or clomiphene for unexplained infertility. The New England Journal of Medicine 2015; 373(13): 1230-1240. doi: 10.1056/NEJMoa1414827

8. Veltman-Verhulst SM, Hughes E, Ayeleke RO, Cohlen BJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Systematic Review 2016; 19; 2:CD001838. doi: 10.1002/14651858.CD001838.pub5

9. The European IVF-monitoring Consortium (EIM). European Society of Human Reproduction and Embryology (ESHRE), Calhaz-Jorge C, De Geyter C, Kupka MS, de Mouzon J, Erb K et al. Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. Human Reproduction 2017; 32(10): 1957-1973. doi: 10.1093/humrep/dex264

10. Guzick, DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST et al. Sperm morphology, motility, and concentration in fertile and infertile men. The New England Journal of Medicine 2001; 345(19): 1388-1393. doi: 10.1056/NEJMoa003005

11. Van Voorhis BJ, Barnett M, Sparks AE, Syrop CH, Rosenthal G et al. Effect of the total motile sperm count on the efficacy and cost-effectiveness of intrauterine insemination and in vitro fertilization. Fertility and Sterility 2001; 75(4): 661-668. doi: 10.1016/s0015-0282(00)01783-0

12. Cohlen BJ. Should we continue performing intrauterine insemination in the year 2004? Gynecologic and Obstetric Investigation 2005; 59(1): 3-13. doi:10.1159/000080492

13. Kennedy S, Bergqvist A, Chapron C, D’Hooghe T, Dunselman G et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Human Reproduction 2005; 20(10): 2698-2704. doi: 10.1093/humrep/dei135

14. Cissen M, Bensdorp A, Cohlen BJ, Repping S, de Bruijn JP et al. Assisted reproductive technologies for male subfertility. Cochrane Database Systematic Review 2016; 2:CD000360. doi: 10.1002/14651858.CD000360.pub5
15. Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertility and Sterility 2015; 103(3): e9-e17. doi: 10.1016/j.fertnstert.2014.12.093

16. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Human Reproduction Update 2006; 12(6): 685-718. doi: 10.1093/humupd/dml034

17. Berker B, Kahraman K, Taskin S, Sukur YE, Sonmez E et al. Recombinant FSH versus clomiphene citrate for ovarian stimulation in couples with unexplained infertility and male subfertility undergoing intrauterine insemination: a randomized trial. Archives of Gynecology and Obstetrics 2011; 284(6): 1561-1566. doi: 10.1007/s00404-011-1997-4

18. Goverde AJ, McDonnell J, Vermeiden JP, Schats R, Rutten FF et al. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. Lancet 2000; 355(9197): 13-18. doi: 10.1016/S0140-6736(99)04002-7

19. Bensdorp AJ, Cohlen BJ, Heineman MJ, Vandekerckhove P. Intra-uterine insemination for male subfertility. Cochrane Database Systematic Review 2007; 18(3): CD000360. doi: 10.1002/14651858.CD000360.pub4

20. Bhattacharya S, Harrild K, Mollison J, Wordsworth S, Tay C et al. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. British Medical Journal 2008; 337: a716. doi: 10.1136/bmj.a716

21. Wordsworth S, Buchanan J, Mollison J, Harrild K, Robertson L et al. Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost effective? Human Reproduction 2011; 26(2): 369-375. doi: 10.1093/humrep/deq315

22. Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Systematic Review 2012; 9: CD001838. doi: 10.1002/14651858.CD001838.pub4

23. Sicchieri F, Silva AB, Silva ACJSP, Navarro PAA, Ferriani RA et al. Prognostic factors in intrauterine insemination cycles. JBRA Assisted Reproduction 2018; 22(1): 02-07. doi: 10.5935/1518-0557.20180002

24. Werbrouck E, Spiessens C, Meuleman C, D’Hooghe T. No difference in cycle pregnancy rate and cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertility and Sterility 2006; 86(3): 566-571. doi: 10.1016/j.fertnstert.2006.01.044

25. Prado-Perez J, Perez-Rivadeneira E, Sanon-Julien F. The impact of endometriosis on the rate of pregnancy of patients submitted to intrauterine insemination. Fertility and Sterility 2002; 77: S51. doi: 10.1016/S0015-0282(01)03182-X

26. Ghaffari F, Sadatmahalleh SJ, Akhoond MR, Eftekhar Yazdi P, Zolfaghari Z. Evaluating the effective factors in pregnancy after intrauterine insemination: A retrospective study. International Journal of Fertility and Sterility 2015; 9(3): 300-308. doi: 10.22074/ijfs.2015.4544

27. Wu HM, Tzeng CR, Chen CH, Chen PH. Pelvic endometriosis with peritoneal fluid reduces pregnancy rates in women undergoing intrauterine insemination. Taiwanese Journal of Obstetrics and Gynecology 2013; 52(4): 512-515. doi: 10.1016/j.tjog.2013.10.010

28. Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C et al. Laparoscopic surgery for endometriosis. Cochrane Database Systematic Review 2014; 4: CD011031. doi: 10.1002/14651858.CD011031.pub2

29. Miller DC, Hollenbeck BK, Smith GD, Randolph JF, Christman GM et al. Processed total motile sperm count correlates with pregnancy outcome after intra-uterine insemination. Urology 2002; 60(3): 497-501. doi: 10.1016/s0090-4295(02)01773-9

30. Patel P, Carrasquillo R, Madhusoodanan V, Dadoun S, Patel A et al. Impact of abnormal sperm morphology on live birth rates following intrauterine insemination. Journal of Urology 2019; 101097/BU00000000000000288. doi: 10.1097/ JU.00000000000000288

31. Cohlen B, Bijkerk A, Van der Poel S, Ombelet W. IUl: review and systematic assessment of the evidence that supports global recommendations. Human Reproduction Update 2018; 24(3): 300-319. doi: 10.1093/humupd/dmx041