Success Rate of Inseminations Dependent on Maternal Age? An Analysis of 4246 Insemination Cycles

Wie viele Inseminationen sind in welchem Lebensalter sinnvoll? Eine Analyse von 4246 Inseminationszyklen

Authors M. Schorsch[1], R. Gomez[2], T. Hahn[1], J. Hoelscher-Obermaier[2], R. Seufert[2], C. Skala[2]

Affiliations
[1] MVZ Kinderwunschzentrum Wiesbaden GmbH, Wiesbaden
[2] Frauenklinik, Universitätsmedizin, JGU Mainz, Mainz

Key words
- insemination
- infertility
- reproductive medicine
- pregnancy

Schlüsselwörter
- Insemination
- Infertilität
- Reproduktionsmedizin
- Schwangerschaft

Abstract

Intrauterine insemination (IUI) has latterly become less important in reproductive medicine. The aim of this retrospective analysis was to identify and evaluate the success rates of repeated insemination cycles in women of different ages. All women who underwent intrauterine insemination in the Wiesbaden Fertility Clinic between 1998 and 2010 were included in the analysis. Additional inclusion criteria were: not more than 45 years old, previous FSH stimulation and slight to moderate subfertility of the male partner. A total of 4246 insemination cycles in 1612 patients were included in the analysis. The average number of IUI cycles per patient was 2.24 (1–14). Patient age ranged from 19 to 45 years (mean: 33.9 years). Logistic regression analysis showed a drop in pregnancy rates with increasing age ($p = 0.000$). However, for the first three cycles the pregnancy rates for women aged 40 and 41 did not differ from those of women aged between 35 and 39 years. Overall pregnancy rates were stable in women up to the age of 40, even after several insemination cycles (7.5 and 10%). Insemination is therefore still an effective procedure in selected patients. Stable pregnancy rates were recorded even after more than 3 cycles. After 3 cycles, the success rates for women aged 40 and 41 did not differ from those of women below the age of 40.

Zusammenfassung

Die intrauterine Insemination (IUI) hat in der Reproduktionsmedizin an Bedeutung verloren. Anhand einer großen Anzahl von Inseminationszyklen soll nun in der folgenden retrospektiven Analyse die Sinnhaftigkeit der wiederholten Insemination bei Frauen unterschiedlichen Alters herausgearbeitet werden. Dazu wurden von allen Patientinnen, die sich von 1998 bis 2010 im Kinderwunschzentrum in Wiesbaden einer homologen Insemination unterzogen, die in die Analyse eingeschlossen, die maximal 45 Jahre alt waren, die mit FSH stimuliert wurden und bei deren Partner eine leichte bis mäßige Subfertilität vorlag. Es handelte sich um 4246 Inseminationszyklen an 1612 Patientinnen. Die durchschnittliche Anzahl der durchgeführten IUI-Zyklen pro Patientin lag bei 2,24 (1–14). Die Patientinnen waren 19–45 Jahre alt (median 33,9 Jahre). In der logistischen Regression zeigte sich eine Verschlechterung der Schwangerschaftsraten mit zunehmenden Alter ($p = 0{,}000$). Dennoch unterscheiden sich die Schwangerschaftsraten der Patientinnen mit 40 und 41 Lebensjahren in den ersten 3 Zyklen nicht von den Patientinnen zwischen 35 und 39 Jahren. Insgesamt zeigen sich bis zum 40. Lebensjahr stabile Schwangerschaftsraten auch nach mehreren Zyklen (7,5 und 10%). Die Insemination stellt bei passender Indikation nach wie vor ein effektives Verfahren dar. Auch nach mehr als 3 Zyklen sind noch stabile Schwangerschaftsraten zu verzeichnen. 40- und 41-jährige Patientinnen unterscheiden sich nach 3 Zyklen in ihrer Erfolgsrate nicht von den unter 40-Jährigen.

received 4.4.2013
revised 25.4.2013
accepted 7.5.2013

Bibliography
DOI http://dx.doi.org/10.1055/s-0033-1350615
Geburtsh Frauenheilk 2013; 73: 808–811 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0016-5751

Correspondence
Dr. Christine Skala
Universitätsmedizin, JGU Mainz
Frauenklinik
Langenbeckstraße 1
55131 Mainz
skala@uni-mainz.de

Introduction

The term "intrauterine insemination" (IUI) is used to describe the transfer of sperm into the uterus. It is one of the oldest techniques of reproductive medicine, first performed in 1790 by the English physician Dr. John Hunter and described by Home in 1799 [1]. The current practice of intrauterine insemination comprises sorting and washing the sperm, determining the optimal time of conception and introducing the sperm into the uterine cavity. In many cases, women additionally undergo controlled ovarian stimulation to trigger ovulation. The prerequisite for successful insemination is an intact tubular and uterine transport system, sufficient numbers of healthy sperm, and guaranteed ovulation. Intrauterine insemination should not lead to any delay in attempting more effective procedures.

Intrauterine insemination is less widely used than other, more effective but much more invasive procedures in reproductive medicine such as in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). In 2008, 21 000 IUI cycles were carried out in Germany in addition to 42 958 IVF and ICSI cycles [2]. Intrauterine insemination can be a successful procedure in selected patients. Acceptance of IUI by patients is high as it is similar to natural insemination and is perceived to be a less invasive intervention in the couple's reproductive life.

Since 2004, § 27 a of the SGB V (German Code of Social Law) requires statutory heath insurance companies in the Federal Republic of Germany to contribute to the costs of 3 insemination cycles after previous stimulation with follicle-stimulating hormone FSH in married couples where the woman is below the age of 40 and the man is below the age of 50. Using the data from a large number of insemination cycles this study aimed to evaluate the impact of maternal age and number of insemination cycles on the success rates for insemination.

Method

Between 1998 and 2010, the Wiesbaden Fertility Clinic carried out a total of 6053 homologous intrauterine inseminations in 2262 patients. Insemination was only done after previous examination found no indications of tubular damage. All patients were ovulating, either as part of their natural cycle, or following low-dose FSH stimulation or stimulation with clomifene. Ovulation was triggered by the administration of human chorionic gonadotropin (hCG).

Inclusion criteria for this retrospective analysis were a maximum patient age of 45 years, limited sperm motility of the patient's partner and stimulation with FSH. A total sperm count of at least 10 million/ml and a motility of at least 35% were required for insemination. A total of 4246 insemination cycles in 1612 women were included in the analysis. The average number of IUI cycles per patient was 2.24 (1–14). In this patient cohort, 158 patients became pregnant more than once through insemination. A second insemination after a previous pregnancy was classified as a first cycle, so that 1770 "treated cases" were evaluated overall. Previous treatments in other fertility clinics were not included in this analysis.

Preparation of the ejaculate consists of washing and the swim-up technique. Washing of the ejaculate is done to separate sperm cells from seminal plasma. Washing is done by mixing and centrifuging the ejaculate with a culture medium. After the heavier spermatozoa collect at the bottom, the remaining liquid are siphoned off and the spermatozoa are mixed and diluted with another culture medium for direct use. In a further preparation step termed "swim-up", the washed semen is centrifuged again and the supernatant siphoned off. The remaining sperm are mixed with a culture medium. The motile sperm swim upwards and can be directly aspirated with a catheter [3].

The insemination cycles were analysed retrospectively. Patient age, number of insemination cycles carried out till pregnancy or until this form of treatment was abandoned and pregnancy rates were included in the analysis. The study was approved by the Ethics Commission of the Johannes-Gutenberg University. All patients gave their informed consent to the study.

Aim of the study was to identify the benefit of repeated insemination cycles for women in different age groups. Statistical analysis was done using the statistical software programme SPSS 18. Logistic regression analysis was used to calculate the impact of maternal age on becoming pregnant. The odds ratio was calculated. The level of significance α was set at 5%.

Results

Average patient age was 33.9 years at the start of therapy. Age range of patients was from 19 to 45 years. Patients were grouped into age groups to show age distribution. Both the pregnancy rates per cycle and the pregnancy rates per patient decreased significantly with increased age (**Table 1**).

Patient age had a statistically measurable impact on pregnancy rates. Logistic regression analysis showed a drop in pregnancy rates with increasing age ($p = 0.000$, CI: 0.905–0.962). The likelihood of becoming pregnant after insemination dropped by 6.7% in the analysed age groups, with an odds ratio of 0.933 per additional year of life.

Younger women had fewer insemination cycles than older women. Patients below the age of 25 years underwent an average of 1.91 cycles while women aged more than 43 years had an average of 2.42 cycles (**Table 1**). Pregnancy rates remained stable even after several insemination cycles. Up until cycle 7, pregnancy rates were between 7.5 and 10%. The number of patients

Table 1 Pregnancy rate as a function of age.

Age (years)	< 24	25–29	30–34	35–39	40, 41	42, 43	> 43
Patients	32	260	687	658	94	27	12
Total number of cycles	61	564	1 650	1 652	222	64	29
Mean number of cycles	1.91	2.17	2.40	2.52	2.36	2.37	2.42
IUI without pregnancy	49	491	1 470	1 506	202	60	28
IUI with pregnancy	12	73	180	146	20	4	1
Pregnancy rate/cycle(%)	19.67	12.94	10.91	8.84	9.01	6.25	3.45
Pregnancy rate/patient (%)	37.5	28.02	26.20	22.19	21.28	14.81	8.33

who underwent more than 3 cycles had already dropped significantly by the 4th cycle (**Table 2**).

Table 3 shows the pregnancy rates per insemination cycle depending on maternal age. It is notable that the pregnancy rates of patients aged 40 and 41 did not differ from those of patients aged between 35 and 39. The success rates were similar for both groups up until the 3rd cycle. This is also shown in **Fig. 1** which depicts the cumulative pregnancy rates for each age group.

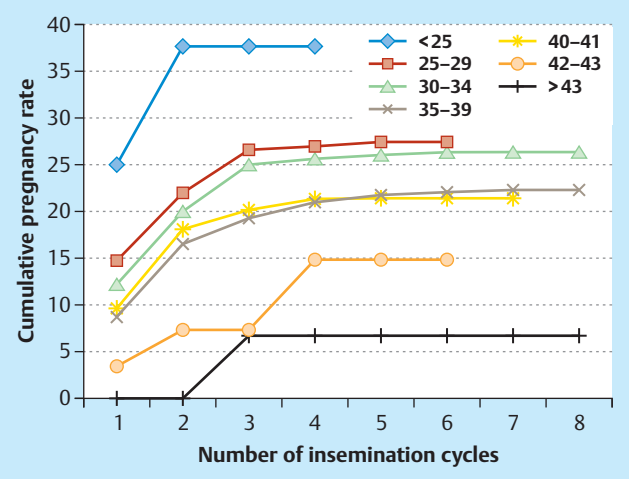

Fig. 1 Cumulative pregnancy rates after each insemination cycle for the different age groups.

Discussion

Age has an important impact on the success rates after insemination. The pregnancy rate per patient was significantly higher for women below the age of 25 compared to women aged 35 to 39. Pregnancy rates gradually decrease over the course of a patient's life. The difference between the youngest group of patients aged less than 25 years and the next group aged between 25 and 29 was very noticeable. There was a similar drop in pregnancy rates in the group aged more than 41 years compared to the group of patients aged 40 or 41. In the group of patients aged 40 and 41 there was still a concrete likelihood of becoming pregnant comparable to that for the group aged 35 to 39. Up until the 3rd cycle, the pregnancy rates of patients aged 40 or 41 did not differ from those of patients between 35 and 39 years of age. These data show that insemination therapy is still justified in patients aged 40 and 41. The data presented here confirm the results of many other studies [4–7], which have all described the impact of increasing age on the success of insemination.

Among the group of patients below the age of 25, no further pregnancies occurred after 2 insemination cycles. This could be an indication that their unfulfilled wish to have a child could have another cause, for example, that male subfertility was more pronounced than originally supposed. Our data suggest that it may not be useful to carry out more than 2 insemination cycles in these young patients. In all other patient groups below the age of 40, pregnancy rates per cycle averaged between 5 and 15% up until the 6th insemination. In women aged more than 40, only a few pregnancies were achieved after 3 insemination cycles. Custers et al. [8] have also shown that even after several insemination cycles the pregnancy rates can be quite good. Other studies, however, have reported a strong decrease in pregnancy rates after only a few cycles [4, 9–11]. The data used in this study suggested that 6 insemination cycles can be recommended for patients aged between 30 and 40, while in patients aged more than 40 only isolated pregnancies occur after the 3rd attempt. Other working groups have recommended between 3–9 insemination cycles per couple [8–10].

The interpretation of the data in this study is complicated by the fact that out of a total of 1770 patients, only 218 underwent more than three attempts at insemination. This is most probably due to the fact that since 2004 statutory health insurance companies in Germany are not obliged to fund more than 3 cycles. The 4th to 6th insemination cycles continued to result in good pregnancy rates in women below the age of 40; however, the patient cohort

Table 2 Pregnancy rates per insemination cycle, 4 262 cycles.

Number of IUI cycles	1	2	3	4	5	6	7	>7
Total number of women	1 770	1 298	811	218	90	39	13	7
IUI without pregnancy	1 575	1 158	747	196	81	35	12	7
IUI with pregnancy	198	140	64	22	9	4	1	0
Pregnancy rate	11.16	10.74	7.82	10.0	10.0	10.26	7.69	0

Table 3 Pregnancy rates per insemination cycle for the different age groups.

Number of IUI cycles	1	2	3	4	5	6	7	>7
< 25 years	25	21.05	0	0				
25–29	14.62	10.86	11.54	15.79	25.00	0		
30–34	12.08	11.18	9.55	6.58	6.90	15.38	0	0
35–39	8.66	10.16	5.38	11.96	13.04	11.11	14.29	0
40 + 41	9.57	12.70	6.06	5.56	0	0	0	
42 + 43	3.70	4.17	0	28.57	0	0		
> 43	0	0	9.09	0	0	0	0	0

undergoing these insemination cycles was significantly smaller than that in the first 3 cycles.

Currently, statutory health insurance companies in Germany contribute to the costs of 3 insemination cycles after stimulation with FSH in women up to the age of 40. Our data shows that pregnancies in these patients can still result after additional insemination cycles. The chances of success for these later cycles correspond to those for the first 3 insemination cycles. In patients aged 40 and 41, a successful pregnancy is most likely with 3 insemination cycles. After more than 3 insemination cycles, pregnancies only occurred in isolated cases.

Conclusion

Intrauterine insemination can be a promising therapy in selected patients. Pregnancy rates for patients aged 40 years remained stable even after more than 3 cycles, up until 6 cycles. For the first 3 insemination cycles, the success rates for women aged 40 and 41 did not differ from those of women under 40. However, no more than 3 insemination cycles should be attempted in these women.

The overall pregnancy rates after insemination were 5–15% and thus clearly lower than those obtained with more invasive reproductive methods such as IVF or ICSI, as demonstrated by data from the German IVF Registry [2]. Patients seeking to become pregnant should be given detailed information about this point. It could play an important role in the choice of method by older couples.

Conflict of Interest

None.

References

1 *Home E.* An Account of the Dissection of an Hermaphrodite Dog. Philosophical Transactions of the Royal Society 1799; 162

2 *Kupka MS, Bühler K, Dahncke W et al.* Summary of the 2008 annual report of the German IVF Registry. J Reproduktionsmed Endokrinol 2010; 7: 34–38; http://www.deutsches-ivf-register.de/pdf-downloads/paper-Kupka-summary.pdf; last access: 2013

3 *Boomsma CM, Heineman MJ, Cohlen BJ et al.* Semen preparation techniques for intrauterine insemination. Cochrane Database Syst Rev 2007; 4: CD004507

4 *Merviel P, Heraud MH, Grenier N et al.* Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. Fertil Steril 2010; 93: 79–88

5 *de Mouzon J, Goossens V, Bhattacharya S et al.* Assisted reproductive technology in Europe, 2006: results generated from European registers by ESHRE. Hum Reprod 2010; 25: 1851–1862

6 *Schröder AK, Pelikan S, Tauchert S et al.* Prognostische Faktoren für den Erfolg einer intrauterinen Insemination: Eine Evaluation von 1005 Zyklen bei 349 Frauen. Geburtsh Frauenheilk 2004; 64: 1052–1060

7 *Stone BA, Vargyas JM, Ringler GE et al.* Determinants of the outcome of intrauterine insemination: analysis of outcomes of 9963 consecutive cycles. Am J Obstet Gynecol 1999; 180 (6 Pt 1): 1522–1534

8 *Custers IM, Steures P, Hompes P et al.* Intrauterine insemination: how many cycles should we perform? Hum Reprod 2008; 23: 885–888

9 *Aboulghar M, Mansour R, Serour G et al.* 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

10 *Peuker A, Hitzl W, Jäger T et al.* Homologe intrauterine Insemination. Gynäkologische Endokrinologie 2007; 5: 97–101

11 *Nuojua-Huttunen S, Tomas C, Bloigu R et al.* Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. Hum Reprod 1999; 14: 698–703

Deutschsprachige Zusatzinformationen online abrufbar unter: www.thieme-connect.de/ejournals/toc/gebfra.