Reproductive BioMedicine Online (2010) 21, 700–705

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# Septate, subseptate and arcuate uterus decrease pregnancy and live birth rates in IVF/ICSI

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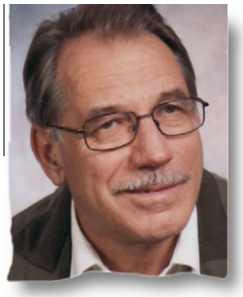

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**Abstract** A retrospective matched-control study to evaluate the effect of uterine anomalies on pregnancy rates after 2481 embryo transfers in conventionally stimulated IVF/intracytoplasmic sperm injection (ICSI) cycles. The study group of 289 embryo transfers before and 538 embryo transfers following hysteroscopic resection of a uterine septum was compared with two consecutive embryo transfers in the control group. Groups were matched for age, body mass index, ovarian stimulation, embryo quality, IVF or ICSI and infertility aetiologies. Number of embryos transferred, embryo quality and absence of uterine anomalies significantly predicted the pregnancy rates in the study group: odds ratios (OR) 1.7, 2.6 and 2.5, respectively ($P < 0.001$). Pregnancy rates after embryo transfer before hysteroscopic metroplasty were significantly lower, both in women with subseptate and septate uterus and in women with arcuate uterus compared with controls. If two or three embryos with at least one best-quality embryo were transferred, the differences were 9.6% versus 43.6%, OR 7.3 ($P < 0.001$) and 20.9% versus 35.5%, OR 2.1 ($P < 0.03$), respectively. Differences in terms of live birth rates were even more evident: 1.9% versus 38.6%, OR 32 ($P < 0.001$) and 3.0% versus 30.4%, OR 14 ($P < 0.001$). After surgery, the differences disappeared.



**KEYWORDS:** arcuate uterus, IVF/ICSI, live birth rate, pregnancy rate, septate uterus, subseptate uterus

## Introduction

The views on the clinical importance of uterine anomalies in human reproduction have recently been altered (Cohen et al., 2007). The literature analysing the influence of uterine anomalies on the results of natural reproduction provides the information that hysterscopic metroplasty improves fertility in women with otherwise unexplained primary infertility (Mollo et al., 2009; Pabuçcu and Gomel, 2004). The literature analysing the influence of uterine anomalies on the results of assisted reproduction provides

1472-6483/$ - see front matter 
doi:10.1016/j.rbmo.2010.06.028

contrasting information (Mollo et al., 2009). On the one hand, Marcus et al. (1996) in a retrospective study comparing IVF results in women with untreated uterine anomalies to women in the general infertile population found similar results, whereas on the other hand, Lavergne et al. (1996) in a retrospective multicentre study comparing the IVF results in women with untreated uterine anomalies to women in the general infertile population found significantly lower implantation and pregnancy rates. Previous studies based on self control design, examining reproductive performance before and after surgery, showed that septate, subseptate and arcuate uterus increased the risk of spontaneous abortion, negatively influenced the implantation and consequently decreased the live birth rates in IVF/intracytoplasmic sperm injection (ICSI) (Tomazevic et al., 2005a, b). Ozgur et al. (2007) showed that a history of pregnancy loss and of IVF failure was more frequent in women with untreated incomplete uterine septum compared with the general infertile population.

In order to further evaluate the problem of decreased live birth rates in women with uterine anomalies; two matched case-control studies were designed. Ban-Frangez et al. (2009) evaluated the influence of subseptate, septate and arcuate uterus on the abortion rates in singleton pregnancies after IVF/ICSI. The abortion rate in IVF/ICSI singleton pregnancies before hysteroscopic metroplasty was significantly higher, both in the women with a small partial septum of arcuate uterine abnormality (OR 12.08) as well as in those with a larger septum (OR 25.00) compared with the women with a normal uterus. After surgery, the abortion rate was comparable to that in women with a normal uterus. The present study analysed the influence of subseptate, septate and arcuate uterus on pregnancy rates after embryo transfer and therefore also implantation in conventionally stimulated IVF/ICSI embryo-transfer cycles.

## Materials and methods

This retrospective matched case-control study was conducted using data from the IVF/ICSI registry of the Department of Obstetrics and Gynecology, University Medical Centre, Ljubljana. The registry included detailed information related to IVF/ICSI procedures and pregnancy outcomes. Data were collected prospectively and updated regularly using Microsoft Excel (Microsoft Corporation, Redmond, Washington).

The study included 2481 embryo transfers in conventionally gonadotrophin-releasing hormone analogue or antagonist/FSH-stimulated IVF or ICSI cycles (Meden-Vrtovec et al., 2003; Virant-Klun et al., 2003). In the study group, 827 embryo transfers were performed: 289 embryo transfers before hysteroscopic resection, 113 of larger septum and 176 of small partial uterine septum, and 538 embryo transfers following hysteroscopic resection, 275 of a large septum and 263 of small partial septum.

For each embryo transfer in the study group, two consecutive embryo transfers were found from the IVF/ICSI registry in women with a normal uterus. The 827 embryo transfers in women of the study group were matched for age, body mass index, stimulation protocol, quality of embryos, use of IVF or ICSI and for infertility indication to 1654 embryo transfers in women of the control group without uterine anomalies. All hysteroscopic resections in women with uterine septum were performed with a resectoscope using a monopolar electric knife. After cervical dilatation, the septum was dissected using a continuous flow resectoscope (Karl Storz, Tuttlingen, Germany). Five percent dextrose was used as a distending medium and the automated gravitational Vario Flow System as the distending system (Tomazevic et al., 1998). The data on the septum length were obtained during hysteroscopic resection by comparing the length of the 1.3 cm long yellow tip of the electronic knife to the length of the resected septum. If the uterine septum measured 1.3–1.5 cm in length it was defined as small (Ban-Frangez et al., 2009; Tomazevic et al., 2007). All uterine anomalies were diagnosed by means of two-dimensional ultrasound examination without intrauterine saline infusion. The normal external uterine shape was ultrasonically confirmed in all the cases. The diagnosis was further confirmed during hysteroscopic procedure (Ban-Frangez et al., 2009; Tomazevic et al., 2007).

During the period 1993–1998, embryo transfer of a maximum of three embryos on day 4, and during the period 1999–2004, embryo transfer of a maximum of two embryos on day 5 was performed. Consequently, in the two periods of time, the criteria for the best embryo quality and for the suboptimal embryo quality were different. In 311 embryo transfers of the study group and in 622 embryo transfers of the control group (1993–1998), morula on day 4 was defined as the best-quality embryo and cleavage-stage embryo as a suboptimal-quality embryo. In 516 cycles of the study group and in 1032 cycles of the control group (1999–2004), blastocyst on day 5 was defined as the best-quality and morula as a suboptimal-quality embryo.

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS, Chicago, USA). Chi-squared test and multivariate logistic regression analysis models were used for statistical analysis. Multivariate logistic regression analysis of the study group included different parameters: resection and non resection of the uterine septum, the length of uterine septum 1.3–1.5 cm and $\geq$1.5 cm, woman's age $<$39 versus $\geq$39 years, IVF or ICSI, transfer of two or three versus one embryo, transfer of the best-quality embryo versus suboptimal-quality embryo. Statistical significance was set at $P < 0.05$.

The primary outcome measures of the present study were clinical pregnancy rates and the secondary outcome measures were live birth rates. The negative influence of uterine anomalies on pregnancy rates was supposed to be an additional factor for reduced live birth rates in IVF/ICSI.

## Results

Following 2481 embryo transfers in the study and the control group, there were 613 (24.7%) clinical pregnancies which ended in 460 (18.5%) live births. Among them there were 387 singletons, 72 twins and one triplet. There were 139 (5.6%) abortions and 14 (0.6%) ectopic pregnancies. The abortion rate was significantly higher in the study group before the operation compared with the control groups (77.1% versus 16.7%, $P < 0.001$). After surgery the differences in abortion rates compared with control groups disappeared (29.2%

**Table 1** Analysis of factors possibly influencing intrauterine pregnancy rates in the study group of 827 embryo transfers in women before and after surgery for uterine septum in conventionally stimulated IVF/ICSI cycles using multivariate logistic regression.

| *Variable* | *Odds ratio* | *95% CI* | *P-value* |
|---|---|---|---|
| Embryo transfer before surgery versus after surgery | 2.507 | 1.529–4.111 | <0.001 |
| Septate versus arcuate uterus | 0.833 | 0.581–1.195 | NS |
| Age <39 versus ≥39 years | 0.993 | 0.950–1.037 | NS |
| IVF versus ICSI | 0.748 | 0.512–1.094 | NS |
| Two or three versus one embryo transferred[a] | 1.676 | 1.040–2.702 | 0.034 |
| Optimal versus suboptimal-quality embryo transferred[b] | 2.578 | 1.747–3.804 | <0.001 |

ICSI = intracytoplasmic sperm injection; NS = not statistically significant.
[a]1993–1998 maximum three embryos transferred; 1999–2005 maximum two embryos transferred.
[b]1999–1998 morula versus cleavage-stage embryo on day 4; 1999–2005 blastocyst versus morula on day 5.

versus 18.4%). These results are in agreement with those of the previous study showing higher abortion rates before hysteroscopic resection of the uterine septum in women with septate and subseptate uterus (OR 25.00) and in women with arcuate uterus (OR 12.8) (Ban-Frangez et al., 2009).

The results in terms of pregnancy and live birth rates are presented in **Tables 1–5**. Multivariate logistic regression analysis of the study group showed that the number of embryos transferred (two or three versus one), quality of embryos transferred and absence of a uterine septum

**Table 2** Comparison of different variables of the study and the control groups.

| *Variable* | *Study* | *Control* |
|---|---|---|
| Large septum (septate and subseptate) before resection | | |
| *n* | 113 | 226 |
| Age | 32.8 ± 2.9 | 32.8 ± 2.6 |
| BMI | 23.5 ± 1.6 | 22.8 ± 2.8 |
| No. of embryos transferred[a] | 1.79 ± 0.40 | 1.79 ± 0.40 |
| Optimal embryo quality[b] | 61 (54.0) | 119 (52.7) |
| ICSI | 22 (19.5) | 43 (19.0) |
| Small partial septum (arcuate uterus) before resection | | |
| *n* | 176 | 352 |
| Age | 31.9 ± 3.5 | 31.9 ± 3.3 |
| BMI | 22.9 ± 2.3 | 23.3 ± 2.5 |
| No. of embryos transferred[a] | 1.73 ± 0.44 | 1.71 ± 0.46 |
| Optimal embryo quality[b] | 90 (51.1) | 185 (52.6) |
| ICSI | 55 (31.3) | 99 (28.1) |
| Large septum (septate and subseptate) uterus after resection | | |
| *n* | 275 | 550 |
| Age | 33.2 ± 3.8 | 33.2 ± 4.0 |
| BMI | 23.1 ± 2.6 | 22.7 ± 2.9 |
| No. of embryos transferred[a] | 1.75 ± 0.43 | 1.77 ± 0.41 |
| Optimal embryo quality[b] | 147 (53.5) | 299 (54.4) |
| ICSI | 120 (43.6) | 237 (43.1) |
| Small partial septum (arcuate uterus) after resection | | |
| *n* | 263 | 526 |
| Age | 33.4 ± 3.4 | 34.4 ± 4.3 |
| BMI | 23.0 ± 2.9 | 22.9 ± 2.9 |
| No. of embryos transferred[a] | 1.76 ± 0.42 | 1.75 ± 0.44 |
| Optimal embryo quality[b] | 152 (57.8) | 318 (60.5) |
| ICSI | 124 (47.1) | 234 (44.5) |

Values are mean ± SD or *n* (%) unless otherwise indicated. There were no statistically significant differences between the two groups.
[a]1993–1998 maximum three embryos transferred; 1999–2005 maximum two embryos transferred.
[b]1993–1998 morula on day 4 1999–2005 blastocyst on day 5.BMI = body mass index; ICSI = intracytoplasmic sperm injection.

**Table 3** Comparison of infertility aetiologies between the study and control groups.

| *Variable* | *Study* | *Control* |
|---|---|---|
| Large septum (septate and subseptate uterus) before resection | | |
| *n* | 113 | 226 |
| Tubal factor | 88 (77.9) | 163 (72.1) |
| Endometriosis | 43 (38.1) | 95 (42.0) |
| Endocrinological | 18 (15.9) | 27 (11.9) |
| Male factor | 17 (15.0) | 38 (16.8) |
| Idiopathic infertility | 10 (8.8) | 21 (9.3) |
| Small partial septum (arcuate uterus) before resection | | |
| *n* | 176 | 352 |
| Tubal factor | 93 (52.8) | 195 (55.4) |
| Endometriosis | 44 (25.0) | 97 (27.6) |
| Endocrinological | 30 (17.0) | 65 (18.5) |
| Male factor | 47 (26.7) | 74 (21.0) |
| Idiopathic infertility | 12 (6.8) | 17 (4.8) |
| Large septum (septate and subseptate uterus) after resection | | |
| *n* | 275 | 550 |
| Tubal factor | 162 (58.9) | 279 (50.7) |
| Endometriosis | 88 (32.0) | 149 (27.1) |
| Endocrinological | 39 (14.2) | 101 (18.4) |
| Male factor | 72 (26.2) | 176 (32.0) |
| Idiopathic infertility | 17 (6.2) | 41 (7.5) |
| Small partial septum (arcuate uterus) after resection | | |
| *n* | 263 | 526 |
| Tubal factor | 129 (49.0) | 289 (54.9) |
| Endometriosis | 89 (33.8) | 142 (27.0) |
| Endocrinological | 56 (21.3) | 89 (16.9) |
| Male factor | 102 (38.8) | 207 (39.4) |
| Idiopathic infertility | 16 (6.1) | 28 (5.3) |

Values are *n* (%) unless otherwise indicated. There were no statistically significant differences between the two groups.

**Table 4** Analysis of all embryo transfers in the study and in the control groups regardless of the number and quality of embryos transferred (1993–2005).

| *Variable* | *Study* | *Control* | *OR (95% CI)* | *P-value* |
|---|---|---|---|---|
| Large septum (septate and subseptate uterus) before resection | | | | |
| *n* | 113 | 226 | | |
| Pregnancy | 14 (12.4) | 66 (29.2) | 2.917 (1.555–5.470) | 0.001 |
| Live birth | 3 (2.7) | 49 (21.7) | 10.151 (3.270–31.408) | 0.001 |
| Small partial septum (arcuate uterus) before resection | | | | |
| *n* | 176 | 352 | | |
| Pregnancy | 24 (13.6) | 90 (25.6) | 2.176 (1.329–3.561) | 0.002 |
| Live birth | 5 (2.8) | 75 (21.3) | 9.260 (3.777–22.672) | 0.001 |
| Large septum (septate and subseptate uterus) after resection | | | | |
| *n* | 275 | 550 | | |
| Pregnancy | 63 (22.9) | 143 (26.0) | 1.182 (0.842–1.661) | NS |
| Live birth | 43 (15.6) | 115 (20.9) | 1.426 (0.972–2.093) | NS |
| Small partial septum (arcuate uterus) after resection | | | | |
| *n* | 263 | 526 | | |
| Pregnancy | 68 (25.9) | 145 (27.6) | 1.091 (0.780–1.527) | NS |
| Live birth | 49 (18.6) | 115 (21.9) | 1.222 (0.843–1.772) | NS |

Values are *n* (%) unless otherwise indicated.
NS = not statistically significant.

**Table 5** Analysis of embryo transfers in the study and in the control groups. Embryo transfers with two or three embryos (1993–1998) and two embryos (1999–2004) with at least one best-quality embryo transferred.

| *Variable* | *Study* | *Control* | *OR (95% CI)* | *P-value* |
|---|---|---|---|---|
| Large septum (septate and subseptate uterus) before resection | | | | |
| *n* | 52 | 101 | | |
| Pregnancy | 5 (9.6) | 44 (43.6) | 7.256 (2.663–19.771) | 0.001 |
| Live birth | 1 (1.9) | 39 (38.6) | 32.081 (5.363– 189.661) | 0.001 |
| Small partial septum (arcuate uterus) before resection | | | | |
| *n* | 67 | 135 | | |
| Pregnancy | 14 (20.9) | 48 (35.6) | 2.086 (1.051–4.149) | 0.03 |
| Live birth | 2 (3.0) | 41(30,4) | 14.176 (3.648–54.702) | 0.001 |
| Large septum (septate and subseptate uterus) after resection | | | | |
| *n* | 123 | 256 | | |
| Pregnancy | 40 (32.5) | 103 (40.2) | 1.397 (0.889–2.196) | NS |
| Live birth | 30 (24.4) | 82 (32.0) | 1.461 (0.899–2.374) | NS |
| Small partial septum (arcuate uterus) after resection | | | | |
| *n* | 125 | 261 | | |
| Pregnancy | 46 (36.8) | 102 (39.1) | 1.102 (0.780–1.527) | NS |
| Live birth | 35 (28.0) | 84 (32.2) | 1.220 (0.765–1.946) | NS |

NS = not statistically significant.

significantly influenced the pregnancy rate after embryo transfer in IVF/ICSI cycles: OR 1.7 ($P$ 0.034), 2.6 ($P < 0.001$) and 2.5 ($P < 0.001$), respectively. The woman's age, type of fertilization and the size of the uterine septum did not significantly influence the pregnancy rate (**Table 1**).

Comparisons in women's age, body mass index, type of fertilization, quality of the transferred embryo (best quality versus lower quality), the number of embryos transferred (two or three versus one) and different infertility causes showed no significant differences between the groups (**Tables 2 and 3**).

The pregnancy rates before hysteroscopic resection, both in women with a septate or subseptate uterus and in women with a small partial septum of arcuate abnormality were significantly lower compared with those in normal control groups: OR 2.9 ($P < 0.002$) and 2.2 ($P < 0.001$), respectively. After surgery, the pregnancy rate was comparable to the pregnancy rate in women with a normal uterus (OR 1.2 and 1.1) (**Table 4**).

Before hysteroscopic resection, the pregnancy rates after the transfer of two or three embryos with at least one best-quality embryo were also significantly lower, both in women with a subseptate or septate uterus (OR 7.3, $P < 0.001$) and in women with a small partial uterine septum of arcuate abnormality (OR 2.1, $P < 0.03$). After surgery, the pregnancy rate was comparable to that in women with a normal uterus, both in the group of women with a subseptate or septate uterus (OR 1.4) and in women with a small partial septum of arcuate abnormality (OR 1.1) (**Table 5**).

As expected, the live birth rates after embryo transfer of from one to three embryos regardless of the embryo quality before hysteroscopic resection were significantly lower compared with normal controls, both in women with a subseptate or septate (2.7% versus 21.7%) uterus (OR 10.15, $P < 0.001$) and in women with a small partial uterine septum of arcuate abnormality (2.8% versus 21.3%, OR 9.26, $P < 0.001$) (**Table 4**).

The live birth rates after the transfer of two or three embryos with at least one best-quality embryo, before hysteroscopic resection, were also significantly lower both in women with a subseptate or septate uterus (1.9% versus 38.6%, OR 32.08, $P < 0.001$) and in women with a small partial uterine septum of arcuate abnormality (3.0% versus 30.4%, OR 14.18, $P < 0.001$) (**Table 5**).

After surgery, the live birth rate was comparable to that in women with a normal uterus, both in the group of women with subseptate or septate uterus (24.3% versus 32.0%, OR 1.46) and in women with a small partial septum of arcuate abnormality (28.0% versus 32.2%, OR 1.22) and so were the live birth rates (**Table 5**).

## Discussion

According to the literature and previous studies, there are two problems that importantly reduce the live birth rates in IVF/ICSI in women with uterine septae: the problem of significantly higher pregnancy losses and the problem of significantly lower pregnancy rates (Tomazevic et al., 2005a, b; Ozgur, 2007).

In a recently published matched case control study, the problem of higher pregnancy losses was analysed. The present results confirmed previous observations that septate, subseptate and arcuate uterus significantly increase the abortion rate in IVF/ICSI (OR 25.00 and 12.08, respectively) ($P < 0.001$) (Ban-Frangez et al., 2009).

Furthermore, the present data confirm the previous observation that septate, subseptate and arcuate uterus significantly decrease the pregnancy rate after embryo transfer and, therefore, also implantation in conventionally

stimulated IVF/ICSI cycles (Tomazevic et al., 2005a, b). After hysteroscopic surgery, the pregnancy rates were significantly improved and comparable to those in normal controls. The negative influence on the pregnancy rates was even more evident in cycles with two or three embryos and with at least one best-quality embryo transferred (OR 7.3 and 2.09, respectively).

According to presented data, not only surgical correction of the septate or subseptate uterus but also surgical correction of the arcuate uterus represents an important intervention to improve live birth rates in IVF/ICSI. Firstly, to significantly improve the pregnancy outcomes (Ban-Frangez et al., 2009; Grimbizis et al., 2001; Ozgur et al., 2007; Tomazevic et al., 2007) and secondly, to at least double the pregnancy rate in IVF and ICSI.

The data presented do not only support the previous observations (Tomazevic et al., 2005a, b), but also agree with the findings in the literature implying that hysteroscopic resection of the uterine septum improves fertility in women with a septate uterus and otherwise unexplained infertility (Mollo et al., 2009; Pabuçcu and Gomel, 2004). In the present study, the negative impact of the uterine septum on implantation was more evident in women with a septate or subseptate uterus (OR 7.3, $P < 0.001$) than in women with an arcuate uterus (OR 2.1, $P < 0.03$). The negative impact on implantation should be considered as an important argument to treat uterine anomalies in infertile women.

These observations fully agree with the statement that hysteroscopic correction of uterine abnormalities with its simplicity, minimal postoperative sequelae, and improved reproductive outcome should not be used only in women with recurrent pregnancy loss and preterm labour, but also in infertile women to improve pregnancy rates and the live birth rates, especially if IVF is being contemplated (Homer et al., 2000).

## Acknowledgements

The authors would like to thank to coworkers: Mr Sašo Drobnič, MD, Mrs Martina Ribič- Pucelj MD, Ph. D., Mr Adrej Vogler MD, Ph. D., Mr Branko Zorn MD, Ph. D, Mrs Lili Bačer-Kermavner B.Sc., Mrs Brigita Valentinčič B.Sc, Jožica Mivšek biol., Mrs Andreja Peterlin nurse and especially to Mrs Mojca Pirc MA, and Mrs Nataša Petkovšek MA, for language editing. The work was supported by the Slovenian Research Agency, Ministry of Education, Science and Sports, and by the Ministry of Health of the Republic Slovenia, grant number L3—2380.

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*Declaration: The authors report no financial or commercial conflicts of interest.*

Received 21 March 2010; refereed 10 June 2010; accepted 10 June 2010.