

1 “IT’S ALL TOO MUCH” *

2 THE SHADOW OF OVERTREATMENT LOOMS OVER HYSTEROSCOPIC METROPLASTY
3 FOR SEPTATE UTERUS

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19 RUNNING TITLE: Hysteroscopic metroplasty for septate uterus

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23 INTRODUCTION

24 The weather is getting stormy over hysteroscopic metroplasty for septate uterus, as the long-awaited
25 results of the first randomised controlled trial (RCT) on septoplasty have finally been published in this
26 issue of *Human Reproduction* (Rikken *et al.*, 2021). Live birth within 12 months of randomisation, the
27 main outcome measure, occurred in 12 of 39 (31%) women allocated to septum resection and in 14 of
28 40 (35%) women allocated to expectant management. The authors conclude “*in light of the lack of any*
29 *evidence of effectiveness and the potential for harm, we recommend against septum resection as a*
30 *routine procedure in clinical practice*” (Rikken *et al.*, 2021).

31 The contrasts between gynaecologists fostering or opposing the hysteroscopic procedure already
32 sharpened when no benefit of septoplasty on post-operative live birth rate was observed in two recent
33 cohort studies (Rikken *et al.*, 2020a; Whelan *et al.*, 2020a). Indeed, whenever the results of good-
34 quality studies contradicting existing convictions and habits are published, clinicians generally
35 scrutinise protocol details, study conduct and data analysis in search for possible methodological flaws
36 (Alonso Pacheco *et al.*, 2020; Garzon *et al.*, 2020; Rikken *et al.*, 2020b; Saridogan *et al.*, 2020; Whelan
37 *et al.*, 2020b). However, this might dismiss the strong overall message that an RCT, particularly in the
38 surgical field, offers.

39

40 ANATOMICAL PLAUSIBILITY AND BIOLOGICAL GRADIENT

41 The arcuate uterus is not associated with adverse pregnancy outcomes. Contrarily, a partial or complete
42 septate uterus has been associated with an increased risk of miscarriage, suggesting a direct relationship
43 between the degree of uterine cavity bipartition and the probability of pregnancy loss (Akhtar *et al.*
44 2020; Chan *et al.*, 2011; Practice Committee of the American Society for Reproductive Medicine,
45 2016; Venetis *et al.*, 2014). When Fedele *et al.* (1989) studied the evolution of pregnancies exclusively
46 in women with an uncorrected complete septate uterus, the risk of miscarriage was maximum when
47 implantation occurred on the septum, and almost non-existent when it occurred on the lateral uterine

48 wall. This increase in the risk of miscarriage has been traditionally attributed to the macro- and
49 microscopic differences observed between the normal myometrium and the non-resorbed tissue that
50 divides the uterine cavity (Bettocchi *et al.*, 2007; Fascilla *et al.*, 2020). Anomalies in the endometrium
51 covering the septum may also play a pathogenic role (Rikken *et al.*, 2019).

52 More generally, if the septate uterus has an impact on pregnancy, the risk of miscarriage should
53 be proportional to the likelihood of septal implantation. In fact, it seems unlikely that the prognosis is
54 an all-or-none phenomenon based on precise cut-off millimetric measurements, percentages of uterine
55 wall thickness, or degrees of the angle of septal indentation. However, the available evidence does not
56 support such a biological gradient concept (Practice Committee of the American Society for
57 Reproductive Medicine, 2016) and we are only left with the different classification of arcuate and
58 septate uterus.

59

60 WHAT WAS THE ORIGINAL STUDY QUESTION AND WHAT ANSWER CAN THIS RCT
61 PROVIDE?

62 As acknowledged by the authors themselves (Rikken *et al.*, 2018 and 2021), participant recruitment
63 was a major problem encountered during their TRUST trial. This is reflected by the long enrolment
64 period from 2010 to 2018, change from a single- to a multi-centre study in 2015, change in the
65 eligibility criteria from exclusively recurrent pregnancy loss to include subfertility in 2011 and one
66 pregnancy loss only or preterm birth in 2015, and change in the classification adopted for the diagnosis
67 of a septate uterus (Rikken *et al.*, 2018).

68 Whelan *et al.* (2020a) maintain that the TRUST study “*was not designed to definitively answer*
69 *whether hysteroscopy metroplasty is of benefit in the subset of women with recurrent early pregnancy*
70 *loss*”, as women with a history of subfertility or preterm delivery were also included. According to the
71 Practice Committee of the American Society for Reproductive Medicine (2016), “*there is insufficient*

72 *evidence to conclude that a uterine septum is associated with infertility*”, and the National Institute for
73 Health and Care Excellence (NICE), as well the Royal College of Obstetricians and Gynaecologists
74 (RCOG), suggest hysteroscopic metroplasty in women with recurrent miscarriage but not in subfertile
75 women. The association with preterm birth is also controversial (Akhtar *et al.*, 2020; Chan *et al.*, 2011;
76 NICE 2015a and 2015b; Practice Committee of the American Society for Reproductive Medicine,
77 2016; Venetis *et al.*, 2014).

78 In addition, the ESHRE classification (Grimbizis *et al.*, 2013) has been criticized for the risk of
79 overdiagnosis and the limited discrimination potential between arcuate and subseptate uterus compared
80 with the American Fertility Society scheme (The American Fertility Society, 1988). Accordingly, the
81 RCOG suggests using the latter classification (Akhtar *et al.* 2020). If some women with borderline
82 anomalies were also included in this RCT, the effect of hysteroscopic septoplasty might have been
83 diluted (Practice Committee of the American Society for Reproductive Medicine, 2016).

84 Originally, Rikken *et al.*’s RCT was devised as a pilot study “*to assess feasibility for a larger*
85 *adequately powered trial*” (<https://www.isrctn.com/ISRCTN28960271>; accessed on 20 February 2021).
86 The authors calculated the sample size anticipating an improvement in live birth rate from 35% without
87 surgery to 70% with surgery. They stated that such a difference was based on the results of available
88 retrospective studies (Rikken *et al.*, 2018). However, such a 35% difference was initially calculated for
89 women with recurrent miscarriage only and, in theory, might not refer to those with a history of
90 subfertility, a population subset that might not benefit so dramatically from hysteroscopic metroplasty
91 (Akhtar *et al.*, 2020; NICE 2015b; Practice Committee of the American Society for Reproductive
92 Medicine, 2016).

93 Thus, the answer the TRUST trial provides is that a benefit of 35% or more in live birth rate
94 after septoplasty can be confidently excluded in a mixed population including women with a history of

95 recurrent miscarriage, subfertility and preterm birth. The small numbers prevent separate analyses to
96 assess the specific effect of septoplasty in the above three study subgroups.

97

98 HOW LARGE SHOULD BE THE EFFECT SIZE?

99 Beyond statistical significance, the value of any medical intervention is the result of a complex
100 relationship between effect size, risk of harm and cost. The risk of harm of hysteroscopic metroplasty is
101 modest. Rikken *et al.* (2021) observed a single uterine perforation out of 39 procedures (2.6%). The
102 potential consequences of this complication are highly variable. In several large studies the incidence
103 of uterine perforation was very low or non-existent, although non-randomised studies are often
104 conservative in estimating absolute risks of harms (Papanikolaou *et al.*, 2006). Even a procedure with a
105 demonstrable effect could be labelled as “low-value” if the magnitude of the statistically significant
106 incremental benefit achieved is not worthwhile to the health care resources it consumes (Pandya, 2018).
107 The cost of metroplasty performed with standard mechanical instrumentation and conducted under
108 ultrasonographic control, thus avoiding laparoscopy, is modest, as neither endotracheal intubation nor
109 overnight hospital stay are required.

110 With regard to the effect size, Rikken and co-workers (2021) set the between-group difference
111 at 35% and consider that, to detect a smaller improvement of 10% in live births, a new study would
112 need to recruit about 750 women and is thus likely unfeasible. However, how would patients consider
113 differences smaller than 35%, but larger than 10%? As an example, at the usual levels of alpha 0.05
114 and beta 0.20, 122 participants would be needed to detect a 25% difference. Such an effect size might
115 be considered both sufficiently large to justify the procedure, given the little resources consumed and
116 the small risk of harms, and not too large as to practically impede the organisation of another RCT.

117

118 FROM THE OPERATING THEATRE TO THE LABOUR WARD: BEHIND LIVE BIRTH RATE

119 Septate uterus is associated with malpresentation (Akhtar *et al.*, 2020; Practice Committee of the
120 American Society for Reproductive Medicine, 2016). This has been confirmed by Rikken *et al.* in both,
121 their cohort study (2020a) and RCT (2021), although the between-group difference in breech
122 presentation rate was not statistically significant in either. However, as a simple exercise, and bearing
123 in mind the limitation of pooling data from different study types without adjusting for potential
124 confounders, when data on ongoing pregnancies is pulled from Rikken *et al.*'s cohort observational and
125 randomised studies (2020a and 2021), breech presentation was significantly less frequent in women
126 who underwent hysteroscopic metroplasty than in those who underwent expectant management (19%
127 vs 33%; OR 0.43, 95% CI, 0.22 to 0.82. Figure 1).

128 According to the RCOG (2017), breech presentation occurs in 3–4% of term deliveries, is
129 associated with uterine abnormalities, and has a significant recurrence risk. In the Term Breech Trial,
130 perinatal mortality, neonatal mortality, or serious neonatal morbidity was significantly lower for the
131 planned caesarean section group than for the planned vaginal birth group (Hannah *et al.*, 2000).

132 Presumably, nowadays most women would not accept to deliver vaginally when their baby is in
133 breech presentation. Moreover, in case of abdominal delivery because of malpresentation, women with
134 an uncorrected uterine septum would likely undergo repeat caesareans in subsequent pregnancies. On
135 the other hand, a history of uneventful hysteroscopic metroplasty is usually not considered *per se* a
136 contraindication to vaginal delivery, as the very few reported cases of uterine rupture during labour
137 occurred solely when septal incision was excessive with penetration into the myometrium or uterine
138 wall perforation (Practice Committee of the American Society for Reproductive Medicine, 2016).

139 However, estimating the magnitude of the effect of hysteroscopic metroplasty as a
140 malpresentation-reducing procedure in women with septate uterus is problematic because the frequency
141 of breech presentation in the intervention group of both studies conducted by Rikken *et al.* was
142 unusually high (2020a and 2021). Thus, the overall surgical burden encumbered upon women with

143 septate uterus, if they eventually chose to undergo hysteroscopic metroplasty or expectant management,
144 remains to be defined.

145

146 PROSPECTUS: DO WE NEED ANOTHER TRIAL?

147 Rikken and co-workers are to be greatly commended for finally adopting the only adequate
148 scientific and ethical approach to disentangle an important and relatively frequent clinical issue. The
149 community of hysteroscopists should now feel somewhat embarrassed when realising that septoplasty
150 has been introduced into practice without sufficiently robust evidence of effectiveness, although
151 recommendations for producing reliable data on surgical innovation were published more than a decade
152 ago (Bakun *et al.*, 2009; Ergina *et al.*, 2009; McCulloch *et al.*, 2009; McCullough and Jones, 2009). In
153 addition, the authors confirmed that findings of RCTs are generally much less exciting than those of
154 observational studies (Ioannidis *et al.*, 2001; Selman *et al.* 2008).

155 Consequently, should hysteroscopic metroplasty be banned *tout court* without trying to clarify
156 those doubts that remain? One of the main benefits of the current trial is that, from now on, septoplasty
157 will be put under scrutiny all over the world. Contrary to the authors' opinion, it may well turn out that,
158 precisely because of the results of their study, surgeons will eventually become available for RCTs and
159 women more willing to participate. In fact, considering both live births and delivery mode, equipoise
160 still seems to exist, and data from another, larger, RCT might be warranted.

161 In this regard, the ESHRE Special Interest Group in Reproductive Surgery could organise an
162 adequately powered, multi-national trial selectively recruiting women with class U2b anomalies
163 (Grimbizis *et al.*, 2013 and 2016); that is, complete septate uterus. Such a trial would prevent any
164 potential classification bias. Either live birth or caesarean section rate could be selected as the primary
165 outcome. Academic "adversaries" should participate in designing the RCT with the aim of limiting
166 potential investigator bias, and data could be analysed by independent research groups (Leichsenring

167 and Steinert, 2017). Imaging and surgical findings should be rendered publicly available together with
168 trial data.

169 In the meantime, women should be fully informed of all the uncertainties surrounding
170 hysteroscopic metroplasty in different clinical conditions. The possibility that septoplasty may confer
171 only a limited benefit, or no benefit at all, must be clearly revealed. The surgeon should disclose any
172 financial conflict of interest in case the procedure is scheduled. Precisely when the quality of the
173 evidence in favour of surgery is weak, different women may choose differently if adequately informed
174 and empowered (Johnson *et al.*, 2008).

175

176 DATA AVAILABILITY

177 No new data were generated in support of this manuscript. Pooled analysis was based on data reported
178 in two published reports (Rikken *et al.* 2020a and 2021).

179

180 AUTHORS' ROLES

181 P.V. conceived and drafted the original version of the manuscript; F.C and F.P. participated in the
182 conception of the manuscript; all the authors revised critically the article for important intellectual
183 content, and approved the final version of the manuscript to be published.

184

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188 CONFLICT OF INTEREST

189 P.V., F.C., and F.P. declare that they have no conflicts of interest.

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315

316 LEGEND TO FIGURE

317

318 **Figure 1.** Forest plot showing individual and combined effect size estimates and 95% CIs in two
319 studies that evaluated the likelihood of breech presentation in women with a subseptate or septate
320 uterus who underwent hysteroscopic metroplasty or expectant management before the index
321 conception. *Horizontal lines* indicate 95 CIs; *boxes* show the study-specific weight; *rhombus* represents
322 combined effect size.

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