

Treatment and outcome in 370 cases with spontaneous or post-laser twin anemia polycythemia sequence managed in 17 different fetal therapy centers

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1 **Treatment and outcome in 370 cases with spontaneous or post-laser twin anemia polycythemia**
2 **sequence managed in 17 different fetal therapy centers**

3 Short title: Treatment and Outcome in 370 TAPS twins

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45 **CONTRIBUTION**

46 ***What does this work add to what is already known?***

47 Antenatal treatment for TAPS differs considerably amongst fetal therapy centers. Perinatal mortality
48 is comparable for all treatment groups. Severe neonatal morbidity was significantly higher in cases
49 treated with IUT (\pm PET) or delivery. Prolonging pregnancy was best achieved in expectant
50 management, laser surgery and selective feticide.

51

52 ***What are the clinical implications of this work?***

53 There is no international consensus on the best treatment for TAPS. Treatment groups differed greatly
54 at baseline, hampering reliability and generalizability of results. To improve outcome for TAPS, a
55 randomized controlled trial investigating the best treatment option is urgently needed.

56 **KEYWORDS**

57 Monochorionic twins, twin anemia polycythemia sequence, TAPS, treatment, intrauterine transfusion,
58 laser surgery, selective feticide, expectant management

59 **DECLARATION OF INTEREST**

60 The authors report to have no financial nor commercial conflict of interest.

61

62 **Abstract**

63 **Objective:** to investigate antenatal management and outcome in a large international cohort of
64 spontaneous and post-laser twin anemia polycythemia sequence (TAPS).

65 **Methods:** Data of monochorionic twins diagnosed antenatally with TAPS collected in the TAPS Registry
66 between 2014-2019 were included in this study. Antenatal diagnosis of TAPS was based on middle
67 cerebral artery peak systolic velocity (MCA-PSV) > 1.5 Multiples of the Median (MoM) in the TAPS
68 donor and < 1.0 MoM in the TAPS recipient. Cases were assigned to the management groups based
69 on the first treatment that was received. The primary outcome included perinatal mortality and severe
70 neonatal morbidity. The secondary outcome was diagnosis-to-birth interval.

71 **Results:** In total, 370 TAPS cases were antenatally diagnosed and managed either with expectant
72 management in 31% (113/370), laser surgery in 30% (110/370), intrauterine transfusion (IUT) (with or
73 without partial exchange transfusion (PET)) in 19% (70/370), delivery in 12% (43/370), selective
74 feticide in 8% (30/370) or termination of pregnancy in 1% (4/370). Perinatal mortality occurred in 17%
75 (37/225) of the expectant group, in 18% (38/215) of the laser group, in 18% (25/140) in the IUT (\pm PET)
76 group, in 11% (9/86) in the delivery group and in 7% (2/30) of the co-twins in the selective-feticide
77 group ($p = 0.177$). Severe neonatal morbidity was 49% (41/84) in delivery, 46% (56/122) in IUT (\pm PET),
78 31% (60/193) in expectant management, 31% (57/182) in laser surgery and 25% (7/28) in selective
79 feticide ($p = 0.027$). Median diagnosis-to-birth interval was longest after selective feticide (10.5 weeks;
80 IQR: 4.2-14.9), followed by laser surgery (9.7 weeks, IQR: 6.6-12.7), expectant management (7.8
81 weeks; IQR: 3.8-14.4), IUT (\pm PET) (4.0 weeks, IQR: 2.0-6.9 weeks) and delivery (0.3 weeks, IQR: 0.0-
82 0.5), $p < 0.001$. Treatment for TAPS varied greatly within and between the 17 fetal therapy centers.

83
84 **Conclusions:** Antenatal treatment for TAPS differs considerably amongst fetal therapy centers.
85 Perinatal mortality and morbidity were high in all management groups. Prolonging pregnancy was best
86 achieved in expectant management, laser surgery and selective feticide.

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93 **Introduction**

94 Twin anemia polycythemia sequence (TAPS) occurs as the result of chronic unbalanced feto-fetal
95 transfusion through minuscule placental anastomoses in monochorionic twins, leading to anemia in
96 the donor and polycythemia in the recipient¹. Unlike twin-twin transfusion syndrome (TTTS), TAPS
97 develops in the absence of twin oligohydramnios-polyhydramnios sequence (TOPS). TAPS can occur
98 spontaneously in 3-5% of monochorionic twins, or can arise in 2-16% after incomplete laser surgery
99 for TTTS due to the presence of minuscule residual anastomoses^{2,3}.

100 TAPS is a relatively new disease, with its first description originating from 2006⁴. Since then, knowledge
101 of TAPS has greatly increased and insights into pathophysiology, diagnosis and outcome have
102 gradually been established⁵. However, the best antenatal management option for TAPS is still
103 unknown. Options include expectant management, preterm delivery, intrauterine transfusion (IUT) in
104 the donor with or without partial exchange transfusion (PET) in the recipient, fetoscopic laser surgery
105 of the placental vascular anastomoses and selective feticide. Since TAPS is associated with high rates
106 of adverse short- and long-term outcome, it is crucial to investigate which management strategy
107 provides TAPS twins the best outcome⁶⁻⁸. Unfortunately, due to the low incidence of the condition,
108 studies are limited to small numbers, hampering generalizability of results and demanding extreme
109 caution when comparing the outcomes. To generate more substantiated knowledge on the effects of
110 management strategies for TAPS twins, we set up the TAPS Registry, an international collaboration
111 aimed at collecting data on diagnosis, management and outcome in TAPS.

112 The aim of the current study is to investigate perinatal outcome of different antenatal management
113 strategies and to report the antenatal management choices for TAPS in various fetal therapy centers
114 across the world.

115 **Methods**

116 *Registry*

117 The TAPS Registry (www.tapsregistry.org) was established in 2014 as a web-based registry for
118 anonymous data collection. Fetal therapy centers across the world were invited to participate.
119 Participating centers were supplied with personal credentials to enter data of their TAPS cases into
120 the online registry. Between 2014 and 2019, a total of 17 centers contributed to data collection (see
121 list in Appendix 1).

122 *Inclusion criteria*

123 Women were eligible for the study if they were pregnant with monochorionic twins diagnosed with
124 spontaneous or post-laser TAPS. The diagnosis for TAPS was based on a MCA-PSV discrepancy, with

125 an increased MCA-PSV value (>1.5 Multiples of the Median (MoM)) in the TAPS donor combined with
126 a decreased MCA-PSV value (<1.0 MoM) in the TAPS recipient, in absence of TOPS⁹. Cases were
127 excluded if they only had a postnatal diagnosis of TAPS (and were missed antenatally) and/or if they
128 were diagnosed with post-laser TAPS within one week after laser for TTTS, unless TAPS was ongoing
129 after one week and/or if they were first diagnosed with TAPS at stage 5. Of note, the outcome from
130 postnatally diagnosed cases are presented in two other studies investigating outcome in spontaneous
131 and post-laser TAPS separately^{10, 11}.

132 *Collected information*

133 Data on maternal characteristics, diagnosis, management, delivery, placental injection studies, and
134 perinatal outcome were collected. The following information was retrieved from local medical
135 records: gravidity, parity, location of the placenta, moment of diagnosis (ante- or postnatal),
136 gestational age (GA) at diagnosis and TAPS stage at diagnosis. For antenatal management for TAPS,
137 the type of management was recorded: expectant management, preterm delivery, IUT (\pm PET),
138 fetoscopic laser surgery, selective feticide or termination of pregnancy (TOP). For each management
139 decision the GA and TAPS stage were noted, as well as the indication. The severity of antenatal TAPS
140 was determined according to the previously published staging system by Slaghekke et al.¹². For
141 delivery, the following parameters were retrieved: type of delivery (spontaneous or planned), mode
142 of delivery (vaginal or cesarean) and type of cesarean (elective or emergency). Based on placental
143 color dye examination, the type, size and number of placental anastomoses were recorded. Perinatal
144 outcome included: donor/recipient status, hemoglobin and reticulocyte values, treatment with blood
145 transfusion for anemia or partial exchange transfusion for polycythemia on day 1, the presence of
146 severe neonatal morbidities and/or severe cerebral injury and the occurrence of perinatal mortality.

147 *Management-group allocation*

148 We defined the following antenatal management groups for TAPS: expectant management, delivery
149 (defined as a delivery within 7 days after diagnosis), IUT (\pm PET), laser surgery and selective feticide.
150 Since TAPS cases can be managed according to different strategies in the same pregnancy,
151 management-group allocation was based on the first treatment that was performed. The following
152 rules were applied to management-group allocation: cases were assigned to the laser, IUT (\pm PET), or
153 selective-feticide group if that was the first treatment they received within 14 days after diagnosis of
154 TAPS (we allowed a one-week re-examination to confirm the diagnosis of TAPS). If this treatment was
155 performed after 14 days, cases were included in the expectant management group. If cases received
156 laser surgery combined with an IUT during the same procedure, they were assigned to the laser group.

157 When cases had an incomplete laser surgery and other interventions were needed to manage
158 persisting or recurring TAPS, they were assigned to the laser group.

159 *Characteristics for the population*

160 The following parameters were studied for all management groups: type of TAPS (post-laser or
161 spontaneous), location of the placenta, GA at diagnosis, TAPS stage at diagnosis, preterm premature
162 rupture of the membranes (PPROM), GA at PPRM, type of delivery (spontaneous or planned), mode
163 of delivery (vaginal or cesarean), GA at birth, the presence of TAPS postnatally, treatment for postnatal
164 TAPS (defined as a blood transfusion for the donor and/or a partial exchange transfusion for the
165 recipient at birth) and number of survivors per case. The postnatal diagnosis for TAPS was established
166 on the presence of an inter-twin hemoglobin difference > 8.0 g/dL combined with least one of the
167 following: a reticulocyte count ratio > 1.7 or the presence of only minuscule vascular anastomoses
168 detected through color dye injection of the placenta^{13, 14}. Furthermore, we studied specific
169 management-related characteristics for each management group. For expectant management we
170 investigated spontaneous resolution of TAPS (defined as the absence of TAPS postnatally). For IUT
171 (\pm PET), the number of interventions, time interval between interventions (in days), and site(s) of
172 transfusion were examined. In cases with multiple IUT (\pm PET) procedures, the median number of days
173 between interventions was used. For laser surgery we examined recurrent/persistent TAPS, the
174 presence of residual anastomoses, and delivery within 24 hours after the procedure. For selective
175 feticide, donor/recipient status of the treated fetus and the reason for selective feticide were
176 evaluated. For expectant management, IUT (\pm PET), and laser surgery any additional treatment after
177 the initial intervention was recorded.

178 *Primary and secondary outcomes*

179 The primary outcomes of this study were perinatal mortality and severe neonatal morbidity.
180 Secondary outcome was diagnosis-to-birth interval. Outcomes were compared between expectant
181 management, delivery, IUT (\pm PET), laser surgery and selective feticide, for the total group, and for
182 spontaneous and post-laser TAPS separately. Perinatal mortality was defined as fetal demise or
183 neonatal death within 28 days after birth. In the selective-feticide group, perinatal mortality was only
184 reported for the co-twin. Severe neonatal morbidity was defined as the presence of at least one of the
185 following, diagnosed within 28 days after birth or before discharge to home: respiratory distress
186 syndrome requiring mechanical ventilation and surfactant, patent ductus arteriosus requiring
187 treatment, necrotizing enterocolitis \geq stage 2¹⁵, retinopathy of prematurity \geq stage 3¹⁶, amniotic band
188 syndrome, ischemic limb injury or severe cerebral injury. Severe cerebral injury was diagnosed in case
189 of one of the following abnormalities was identified on cerebral imaging: intraventricular hemorrhage
190 \geq stage 3¹⁷, ventricular dilatation (including post-hemorrhagic ventricular dilatation)¹⁸, cystic

191 periventricular leukomalacia \geq grade 2¹⁹, porencephalic or parenchymal cysts, arterial infarction or
192 other severe cerebral lesions associated with adverse outcome.

193 Statistical analyses were carried out using SPSS version 25.0 (IBM, Armonk, NY, USA). Data are
194 presented as medians and interquartile ranges (IQR) or range (minimum-maximum), or n/N (%), as
195 appropriate. A p-value < 0.05 was considered statistically significant. To compare management
196 groups, the outcome in the expectant-management group was set as the reference value. Continuous
197 data on pregnancy level was compared using the one-way ANOVA with Tukey correction. A Chi-square
198 test was used for categorical data on pregnancy-level. To account for the fact that observations
199 between co-twins are not independent, outcomes on fetal or neonatal level were compared using the
200 Generalized Estimated Equation (GEE) module. As a GEE cannot be carried out when an outcome event
201 does not occur in one of the groups, an adjustment to the data was applied. With this adjustment, an
202 unaffected child was changed into an affected child, for all groups. This correction generates more
203 conservative p-values.

204 **Results**

205 Of the 422 TAPS cases that were entered in the TAPS Registry, 10% (43/422) was diagnosed postnatally
206 and excluded from the study. From the remaining 379 cases, nine cases were excluded based on post-
207 laser TAPS diagnosed within one week after laser for TTTS (n = 8) and antenatal TAPS stage 5 at
208 diagnosis (n=1). A total of 370 cases were included in the study. Information on the cases contributed
209 by each fetal therapy are detailed in Appendix 1. Antenatal management consisted of expectant
210 management in 31% (113/370), laser surgery in 30% (110/370), IUT (\pm PET) in 19% (70/370), delivery
211 in 12% (43/370), selective feticide in 8% (30/370) and termination of pregnancy in 1% (4/370). Table
212 1 shows diagnosis-, pregnancy- and delivery-related characteristics for expectant management, laser
213 surgery, IUT (\pm PET), delivery and selective feticide.

214 215 *Expectant management group*

216 The median GA at diagnosis in the expectant management group was 22.6 weeks (IQR: 19.9-27.1,
217 range: 15.1-35.1). The median antenatal TAPS stage at diagnosis was 2 (IQR: 1-2). Spontaneous
218 resolution was seen in 16% (18/111)* of cases that were managed expectantly, and occurred after
219 stage 1 in 17% (9/52), stage 2 in 13% (6/45), stage 3 in 20% (2/11) and in stage 4 in 20% (1/5). In 11%
220 (13/113) of cases, an alternative management strategy was performed after 14 days of expectant
221 management. An IUT (\pm PET) was elected in eight TAPS cases (after 15-97 days from diagnosis), based
222 upon progression of TAPS stage (n = 5), ongoing stage 1 TAPS (n = 2) and initial recovery followed by
223 recurrence of TAPS after 13 weeks (n = 1). In five cases managed expectantly, laser surgery was

224 performed for progression of TAPS (after 15-38 days from diagnosis). In two cases managed with laser
225 surgery, a delivery took place within 24 hours after the procedure, resulting in miscarriage (23 weeks)
226 and premature (28 weeks) birth, with double survival in the latter. In the other three cases, perinatal
227 survival was seen in 5/6 neonates.

228 *Laser surgery group*

229 Laser surgery was performed at a median GA of 22.0 weeks (IQR: 19.5-24.3, range: 16.1-30.1).
230 Spontaneous TAPS cases made up the majority of this treatment group (78%; 86/110). In total, 43%
231 (47/110) of the TAPS cases treated with laser surgery had an anterior placenta. Laser surgery was
232 combined with an IUT in the same procedure in 11% (12/110) of the cases. In 4% (4/108) of cases
233 treated with laser, a delivery took place within 24 hours after the procedure (at 21, 22, 24 and 28
234 weeks). Recurrent TAPS was seen in 15% (16/106) of the cases treated with laser surgery. Out of the
235 16 cases with recurrent TAPS, one was diagnosed with TAPS only postnatally. The remaining 15 were
236 managed expectantly in 2% (3/110), with IUT (\pm PET) in 5% (5/110), laser reintervention in 2% (2/110)
237 and selective feticide in 6% (5/110). In the cases managed expectantly, spontaneous resolution of
238 TAPS was seen in one case. In the other two cases neonatal mortality occurred in three of four liveborn
239 infants. In the recurrent-TAPS cases that were managed with IUT (\pm PET), fetal demise of the donor
240 occurred in two out of the five twins after the first IUT. In both cases the co-twin survived. In the other
241 three cases, two or three IUT (\pm PET) interventions were performed and all infants survived. Both laser
242 reinterventions for recurrent TAPS were successful resulting in perinatal survival of the twins. Five
243 recurrent TAPS cases were treated with selective feticide; four were performed in the donor twin, one
244 in the recipient twin. In one case, fetal demise of the co-twin occurred. Aside from the recurrent-TAPS
245 cases, a selective feticide was performed in two other cases treated with laser surgery, based on
246 severe cerebral injury in the donor detected after laser intervention. In 9% (6/65) of liveborn twin
247 pairs treated with laser surgery, postnatal TAPS was diagnosed. Placental injection information was
248 available in 32% (36/110) of cases treated with laser surgery. Residual anastomoses, which were
249 always minuscule, were detected in 19% (7/36). All cases with residual anastomoses (100%; 7/7) had
250 recurrent TAPS.

251
252 *IUT (\pm PET) group*

253 An IUT (\pm PET) was performed at a median GA of 26.3 weeks (IQR: 23.6-28.8, range: 18.0-32.1). The
254 median antenatal TAPS stage at diagnosis was 2 (IQR: 1-2). An IUT was combined with PET in the
255 recipient in 21% (15/70). In total, 73% (51/70) of the IUT (\pm PET) group had one intervention, 13%
256 (9/70) had two, 7% (5/70) had three, 6% (4/70) had four, and 1% (1/70) had six interventions with IUT
257 (\pm PET). The median time between interventions was 13.0 days (IQR: 8.6-16.8; range: 6.5-21.0). The

258 transfusion site was only intravenous in 70% (15/67), only intraperitoneal in 10% (7/67), and combined
259 in 19% (13/67). An alternative management strategy was decided in 14% (10/70) of the cases treated
260 with IUT (\pm PET). Three cases were treated with laser surgery, all within one week after the first IUT
261 and based on progressive or recurrent TAPS. One laser procedure was complete, the other two were
262 incomplete and both had recurrent TAPS. In seven cases treated with IUT (\pm PET), a selective feticide
263 in the TAPS donor was performed based on recurrent or progressive TAPS (n = 5) or severe cerebral
264 injury (n = 2).

265 *Delivery group*

266 Delivery (within 7 days after diagnosis) took place at a median GA of 31.9 weeks (IQR: 29.1-34.1;
267 range: 26.0-36.0). The median antenatal TAPS stage for cases treated with delivery was 1 (IQR: 1-2).
268 In total, 88% (76/86) had a cesarean section.

269 *Selective feticide group*

270 Selective feticide was performed at a median GA of 22.1 weeks (IQR: 19.9-23.2, range: 17.1-24.6).
271 Reasons for selective feticide included TAPS (67%; 20/30), or TAPS with co-existing: severe growth
272 restriction (10%; 3/30), severe cerebral injury (10%; 3/30), or congenital anomalies (10%; 3/30) In one
273 case, selective feticide was performed on request of the parents (3%; 1/30). In 87% (26/30) of the
274 group, selective feticide was performed in the TAPS donor.

275 *Comparison of outcome between groups*

276 Table 2a provides further information on the outcome for each management strategy. The rate of
277 perinatal mortality was comparable for expectant management (17%; 39/225), laser surgery (18%;
278 38/215), IUT (\pm PET) (18%; 25/140), delivery (11%; 9/86), and selective feticide (7%; 2/30), $p = 0.177$.
279 Severe neonatal morbidity was significantly higher in twins treated with delivery (49%; 41/84) and IUT
280 (\pm PET) (46%; 56/122) than in twins managed expectantly (31%; 60/193), treated with laser surgery
281 (31%; 57/182) or selective feticide (25%; 7/28), $p = 0.027$. Diagnosis-to-birth interval was 7.8 weeks
282 (IQR: 3.8-14.4) in the expectant management group, 9.7 weeks (IQR: 6.6-12.7) after laser surgery and
283 10.5 weeks (IQR: 4.2-14.9) after selective feticide and was significantly shorter in twins treated with
284 delivery (0.3 weeks, IQR: 0.0-0.5) and IUT (\pm PET) (4.0 weeks, IQR: 2.0-6.9), $p < 0.001$. The prevalence
285 of postnatal TAPS was comparable for expectant management (74%; 66/89), IUT (\pm PET) (71%; 36/51),
286 and delivery (84%; 36/43), and significantly lower in twins treated with laser surgery (9%; 6/65), $p <$
287 0.001 . In table 2b and 2c, outcome for management strategies are presented for spontaneous TAPS
288 and post-laser TAPS separately.

289

290 *Management choices for 17 fetal therapy centers*

291 Figure 1 shows management choices for TAPS amongst 17 fetal therapy centers. Overall, management
292 varied considerably. Some centers, like Leiden, Milan and Brisbane, adopt a more conservative
293 attitude and manage a considerable number of cases expectantly. In contrast, London, Paris, and
294 Houston treat TAPS cases more invasively, with laser treatment or selective feticide. Fetal therapy
295 centers in Hamburg and Barcelona generally refrain from doing in-utero interventions and manage
296 the majority of cases expectantly or with delivery. The remaining centers do not show a remarkable
297 trend or preference in management and apply the different treatment options alternately.

298

299 **Discussion**

300 This is the first large international study investigating outcome after antenatal management for TAPS.
301 We found that perinatal mortality and severe neonatal morbidity rates were high in all treatment
302 groups. Management for TAPS varied considerably within and between fetal therapy centers,
303 reflecting the lack of international consensus on the most optimal management strategy. With this
304 study we present new information on treatment for TAPS, thereby providing a more detailed context
305 to management decisions, leading to a more enhanced understanding of TAPS and the clinical
306 implications of each treatment strategy.

307 *Perinatal outcome*

308 Confirming findings from previous smaller studies²⁰⁻²², we found comparable perinatal mortality rates
309 for all management strategies, for the total cohort as well as for spontaneous and post-laser TAPS
310 separately. Notably, post-laser TAPS twins showed substantially higher rates of perinatal mortality
311 than spontaneous TAPS twins in all management groups, illustrating the impact of preceding TTTS on
312 the outcome of twins with post-laser TAPS. Severe perinatal morbidity rates were high in all groups,
313 but were significantly increased in cases treated with IUT (\pm PET) or delivery. Notably, twins managed
314 with IUT (\pm PET) were delivered at a significantly earlier gestation, which is known to have significant
315 impact on short-term outcome^{10, 11}. However, twins that had a delivery were born at a comparable
316 gestation as twins treated with laser, which might suggest that other factors might also play a role.
317 Our results show that expectant management, laser surgery and selective feticide generate a
318 prolongation of pregnancy of 7-10 weeks after the diagnosis of TAPS. A prolonged pregnancy after
319 laser surgery compared to expectant management and IUT (\pm PET) was previously reported by
320 Slaghekke et al.²⁰. Our study shows that TAPS cases treated with IUT (\pm PET) had a significantly shorter
321 diagnosis-to-birth interval. Although gestation can be prolonged by reintervention with IUT (\pm PET),
322 the majority of TAPS cases had only one intervention. A possible explanation could be that due to the
323 relatively high GA at diagnosis, caregivers preferred delivery with subsequent postnatal treatment

324 over continuous exposure of TAPS, as soon as an acceptable gestation was achieved. The shortest
325 diagnosis-to-birth interval was seen in the delivery group, in accordance with the management-group
326 definition.

327 *Optimal treatment?*

328 Determining the most optimal treatment option is crucial to improve outcome in TAPS. Laser surgery
329 is the only management option that directly treats the cause of TAPS, and has shown to drastically
330 improve outcome in TTTS²³. However, laser in TAPS is technically more challenging than in TTTS, due
331 to the absence of TOPS, which may lead to reduced accessibility and visibility of the placental surface.
332 This can be especially problematic in case of an anterior placenta. To optimize technical conditions,
333 TOPS can be artificially created with amnioinfusion in one sac and amniodrainage of the other, but
334 this requires more needle insertions and might increase chances of PPRM and premature birth.
335 However, we report PPRM in 37% and delivery within 24 hours after laser in 4%, which is comparable
336 to laser for TTTS³. A second technical problem comes with the size of TAPS anastomoses, which are
337 known to be minuscule and might therefore be harder to find during procedure. In line, our data
338 showed that TAPS recurred in 15% of cases treated with laser surgery, which is more than twice as
339 high as the recurrence rate of TTTS after laser³. Moreover, we have shown that residual anastomoses
340 after laser for TAPS always lead to the recurrence of the disease. To prevent residual anastomoses and
341 to ensure coagulation of anastomoses that cannot be visualized, the Solomon technique might be of
342 added value³. Nevertheless, the rate of residual anastomoses in TAPS was comparable to the rate of
343 residual anastomoses in TTTS (both 19%),³ and 43% of lasers were performed in cases with an anterior
344 placenta, showing that, despite the practical limitations, laser for TAPS is technically feasible.

345 Although promising in approach, our data show that laser surgery does not seem to improve (nor
346 deteriorate) perinatal outcome when compared to expectant management. However, laser surgery
347 was associated with a high diagnosis-to birth interval, especially in contrast to treatment with IUT (\pm
348 PET). As prematurity has a profound impact on short- and long-term health in TAPS twins, prolonging
349 pregnancy is of utmost importance to improve outcome^{6, 7, 10, 11}. Notably, a comparable prolongation
350 of pregnancy was achieved with selective feticide and expectant management. However, selective
351 feticide comes with a high price, as parents lose at least one baby and do not have a guarantee of
352 healthy survival for the co-twin. Alternatively, in expectant management, prolonging of pregnancy
353 likely results in continuous exposure to potential detrimental effects of TAPS, as only 16% showed
354 spontaneous resolution. As risk for perinatal mortality and morbidity increases with incrementing
355 antenatal TAPS stage, definitive treatment with laser might be the most optimal intervention to
356 improve perinatal outcome for this condition^{24, 25}.

357 One should be extremely cautious with drawing conclusions based on the results of this registry. Due
358 to the retrospective nature of this study, management groups are very likely to be subject to selection
359 bias. As our data have indicated, management groups differed in terms of GA at diagnosis, severity of
360 TAPS, and type of TAPS. Since higher TAPS stages and post-laser TAPS are associated with poorer
361 prognosis, these factors could have significantly influenced perinatal outcome rates^{10, 11}. Moreover,
362 long-term outcome was not investigated in this study. Previous studies have shown that the
363 detrimental effects of TAPS are not limited to the perinatal period, but also manifest later in life^{6, 7}.
364 Therefore, the true effect of management for TAPS can only be properly investigated when TAPS cases
365 are randomized between treatment groups, when stratification for risk factors is applied, and when
366 long-term consequences are taken into account.

367 In conclusion, this registry shows that there is an extensive heterogeneity in management for TAPS,
368 both within and amongst fetal therapy centers. To improve outcome in TAPS, and to generate an
369 international consensus on optimal management, a randomized controlled trial (RCT) is urgently
370 needed. Recently, the TAPS trial, an international multicenter open-label RCT comparing laser surgery
371 to standard care (expectant management, IUT (\pm PET), preterm delivery) has started recruiting
372 patients²⁶.

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Table 1. Diagnosis-, pregnancy-, and delivery-related characteristics for expectant management, laser surgery, IUT (\pm PET), delivery and selective feticide

	Expectant management (N = 113, 226 fetuses)	Laser surgery (N=110, 220 fetuses)	IUT (\pm PET) (N=70, 140 fetuses)	Delivery (N=43, 86 fetuses)	Selective feticide (N=30, 60 fetuses)
GA at diagnosis (weeks)	22.6 (19.9-27.1; 15.1-35.0)	21.7 (19.3-23.9; 16.1-28.9)	25.8 (23.3-28.0; 17.0-32.1)	31.3 (28.6-34.0; 26.0-35.0)	21.4 (19.1-22.9; 15.1-24.0)
GA at intervention (weeks)	-	22.0 (19.5-24.3; 16.7-30.1)	26.3 (23.6-28.8; 18.0-32.1)	31.9 (29.1-34.1; 26.0-36.0)	22.1 (19.9-23.2; 17.1-24.6)
Spontaneous TAPS	51/113 (45)	86/110 (78)	52/70 (37)	34/43 (79)	18/30 (63)
Anterior placenta	55/113 (49)	47/110 (43)	42/70 (60)	22/43 (51)	19/30 (63)
TAPS stage at diagnosis	2 (1-2)	2 (2-3)	2 (1-2)	1 (1-2)	2 (2-3)
1	52/113 (46)	25/110 (23)	18/70 (26)	23/43 (54)	5/30 (17)
2	45/113 (40)	51/110 (46)	37/70 (53)	13/43 (30)	12/30 (40)
3	11/113 (10)	27/110 (24)	10/70 (14)	5/43 (12)	11/30 (37)
4	5/113(4)	7/110 (6)	5/70 (7)	2/43 (5)	2/30 (7)
5	0/113 (0)	-	0/70 (0)		
Alternative treatment	13/113 (11)	16/110 (15)	9/70 (14)	-	-
Expectant		2/110 (2)	-		
IUT (\pm PET)	8/113 (7)	5/110 (5)	-		
Laser (reintervention)	5/113 (4)	2/110 (2)	3/70 (4)		
Selective feticide		7/110 (6)	7/70 (10)		
PPROM	29/113 (26)	40/107 (37) [†]	17/69 (25) [§]	4/43 (9)	13/30 (45)
GA at PPROM (weeks)	29.0 (25.1-31.3; 21.0-36.4)	29.7 (25.9-32.1; 16.9-35.9)	29.0 (25.8-31.5; 17.7-34.0)	29.3 (26.6-33.4; 26.2-34.2)	27.9 (24.8-31.6; 20.2-33.3)
Spontaneous start of delivery	43/113 (38)	60/106 (57) [‡]	20/69 (29) [§]	3/43 (7)	24/29 (83) [¶]
Cesarean	138/226 (61)	160/212 (76) [‡]	100/138 (73)	76/86 (88)	26/58 (46) [¶]

Data are presented as median (IQR; range) or n/N (%). [†] 3 missing values , [‡] 4 missing values (same as ‘†’ plus one case with missing delivery data) [§]1 missing value (one case with missing delivery and PPROM info), [¶] 1 case with missing delivery information

IUT, intrauterine transfusion; GA, gestational age; BT, blood transfusion; PET, partial exchange transfusion; TAPS, twin anemia polycythemia sequence; PPROM, preterm premature rupture of the membranes

Table 2a. Outcome of expectant management, laser surgery, IUT (± PET), delivery, and selective feticide for all TAPS twins

TOTAL GROUP	Expectant management (N = 113 pregnancies; 226 fetuses)	Laser surgery (N= 110 pregnancies; 220 fetuses)	IUT (± PET) (N=70 pregnancies; 140 fetuses)	Delivery (N=43 pregnancies; 86 fetuses)	Selective feticide (N=30 pregnancies; 30 co-twins)	p-value
GA at birth (weeks)	33.0 (30.1-34.9)	31.8 (29.1-34.1)	31.1 (28.3-33.0)*	31.9 (29.1-34.1)	32.1 (27.7-34.8)	<0.001
Diagnosis-to-birth interval (weeks)	7.8 (3.8-14.4)	9.7 (6.6-12.7)	4.0 (2.0-6.9)	0.3 (0-0.5)*	10.5 (4.2-14.9)	< 0.001
Perinatal mortality	39/225 (17) [†]	38/215 (18) [¶]	25/140 (18)	9/86 (11)	2/30 (7) [*]	0.177
Fetal demise	24/226 (11)	28/215 (13)	18/140 (13)	0/86 (0)*	2/30 (7)	0.024
Neonatal Mortality ^ψ	15/201 (8) [†]	10/187 (5) [¶]	7/122 (6)	9/86 (11) [*]	0/28 (0)	0.280
Survivors						
None	5/112 (5) [†]	8/107 (8) [*]	3/70 (4)	1/43 (2)	2/30 (7)	0.359
One	27/112 (24) [†]	20/107 (19)	18/70 (26)	7/43 (16)	28/30 (93)*	<0.001
Two ^ψ	80/112 (71) [†]	78/107 (73)	49/70 (70)	35/43 (81)	0/30 (0)*	<0.001
At least one	108/112 (95) [†]	99/107 (92)	67/70 (96)	42/44 (98)	27/30 (93)	0.304
Severe neonatal morbidity	60/193 (31) [‡]	57/182 (31) [¥]	56/122 (46)	41/84 (49)*	7/28 (25)	0.027
Severe cerebral injury ^ψ	10/193 (5) [‡]	6/182 (3) [¥]	13/122 (11) [*]	8/84 (10)	0/28 (0)	0.098
Postnatal TAPS	66/89 (74)	6/65 (9)*	36/51 (71)	36/43 (84)	-	<0.001
BT/PET at birth for TAPS ^ψ	81/188 (43) [§]	13/171 (8)*£	60/118 (51) [¶]	48/84 (57)	0/23 (0) [◇]	<0.001

Data are presented as median (IQR) or n/N (%). To compare treatments, expectant management was set as a reference. Bold numbers represent significant p-values, an * indicates the smallest p-value that is presented in the p-value column.

† 1 missing value (1 infant with incomplete neonatal outcome) ‡ 8 missing values (same as ‘†’ plus 3 cases that died shortly after birth, and 4 cases with unknown neonatal morbidity), § 13 missing values (same as ‘‡’ plus 5 cases with unknown BT/PET information ¶ 5 missing values ¥ 10 missing values (as ‘¶’ plus 5 cases with missing neonatal outcome) £ 21 missing values (same as ‘¥’ plus 11 cases with missing data on BT/PET at birth), ¶ 4 missing values, ◇ 5 co-twin with missing data on BT/PET

^ψ Statistical correction for non-occurring events is applied

IUT, intrauterine transfusion; GA, gestational age; BT, blood transfusion; PET, partial exchange transfusion; TAPS, twin anemia polycythemia sequence

Table 2b Outcome of expectant management, laser surgery, IUT (± PET), delivery and selective feticide for spontaneous TAPS twins

SPONTANEOUS TAPS	Expectant management (n = 51 pregnancies; 102 fetuses)	Laser surgery (n = 86 pregnancies; 172 fetuses)	IUT (± PET) (n = 26 pregnancies; 52 fetuses)	Delivery (n = 34 pregnancies; 68 fetuses)	Selective feticide (n= 19 pregnancies; 19 co-twins)	p-value
GA at birth (weeks)	33.6 (31.3-35.4)	31.9 (29.1-34.4)	31.3 (30.1-33.1)	32.2 (31.1-34.3)	30.6 (27.2-35.5)*	0.024
Diagnosis-to-birth interval (weeks)	7.7 (2.5-15.4)	10.3 (6.7-14.0)	2.4 (1.3-5.3)	0.3 (0.0-0.8)*	11.1 (3.6-16.3)	<0.001
Perinatal mortality	12/101 (12)†	26/168 (16)¶	2/52 (4)*	5/68 (7)	2/19 (11)	0.118
Fetal demise ^ψ	5/102 (5)	20/168 (12)¶	2/52 (4)	0/68 (0)	2/19 (11)*	0.104
Neonatal Mortality ^ψ	7/96 (7)†	6/148 (4)¶	0/50 (0)*	5/68 (7)	0/17 (0)	0.165
Survivors						
None ^ψ	1/50 (2)	5/84 (6)	0/26 (0)	0/34 (0)	2/19 (11)	0.178
One	8/50 (16)	16/84 (19)	2/26 (8)	5/34 (15)	15/19 (89)*	<0.001
Two ^ψ	41/50 (82)	62/84 (74)	24/26 (92)	29/34 (85)	0/19 (0)*	<0.001
At least one	49/50 (98)	79/84 (94)	26/26 (100)	34/34 (100)	15/19 (89)	0.174
Severe neonatal morbidity	26/93 (28)‡	45/145 (31)¥	22/50 (44)	32/67 (48)* ‡	4/17(24)	0.046
Severe cerebral injury ^ψ	2/93 (2)‡	3/145 (2)	4/50 (8)*	5/67 (8) ‡	0/17 (0)	0.099
Postnatal TAPS	31/46 (67)	4/51 (8)	17/24 (71)	28/34 (82)	-	<0.001
BT/PET at birth for TAPS ^ψ	36/89 (40)§	9/135(7)* £	27/50 (54)	40/67 (60) ‡	0/13 (0) ◊	<0.001

Data are presented as median (IQR) or n/N (%). To compare treatments, expectant management was set as a reference. Bold numbers represent significant p-values, an * represents the smallest p-value that is presented in the p-value column

† 1 missing value (unknown neonatal outcome), ‡ 4 missing values (same as ‘+’ plus 3 cases with unknown neonatal outcome). § 8 missing values (same as ‘‡’ plus 4 cases with missing information on BT/PET at birth ¶ 4 missing values (2 pregnancies missing outcome), ¥ 7 missing values (same as ‘¶’, plus 3 infants with unknown neonatal morbidity). £ 17 missing values (same as ‘¥’ plus 10 infants without BT/PET information), ‡ 1 missing value (one infant died directly after birth) ◊ 5 missing values

^ψ Statistical correction for non-occurring events is applied

IUT, intrauterine transfusion; GA, gestational age; BT, blood transfusion; PET, partial exchange transfusion; TAPS, twin anemia polycythemia sequence

Table 2c Outcome of expectant management, laser surgery, IUT (± PET), delivery and selective feticide for post-laser TAPS twins

POST-LASER TAPS	Expectant management (n = 62 pregnancies; 124 fetuses)	Laser surgery (n = 24 pregnancies; 48 fetuses)	IUT (± PET) (n = 44 pregnancies; 88 fetuses)	Delivery (n = 9 pregnancies; 18 fetuses)	Selective feticide (n= 11 pregnancies; 22 fetuses)	p-value
GA at birth (wks)	32.6 (29.4-34.6)	31.7 (29.1-33.7) §	29.9 (29.0-33.0)*	29.0 (27.7-31.8)	32.6 (31.13-34.0)	0.027
Diagnosis-to-birth interval (wks)	8.0 (4.7-14.3)	8.1 (5.9-11.4)	4.8 (2.5-8.9)	0.3 (0.2-0.4)*	10.4 (9.2-14.4)	<0.001
Perinatal mortality ^ψ	27/124 (22)	12/47 (26) §	23/88 (26)	4/18 (22)	0/11 (0)*	0.217
Fetal demise ^ψ	19/124 (15)	8/47 (17) §	16/88 (18)	0/18 (0)*	0/11 (0)*	0.268
Neonatal Mortality ^ψ	8/105 (8)	4/39 (10)	7/72 (10)	4/18 (22)*	0/11 (0)	0.040
Survivors						
None ^ψ	4/62 (7)	3/23 (13)	3/44 (7)	1/9 (11)	0/11 (0)	0.111
One	19/62 (31)	4/23 (17)	16/44 (36)	2/9 (22)	11/11 (100)*	<0.001
Two ^ψ	39/62 (63)	16/23 (70)	27/44 (57)	6/9 (67)	0/11 (0)*	<0.001
At least one	58/62 (93)	20/23 (87)	41/44 (93)	8/9 (89)	11/11 (100)	0.111
Severe neonatal morbidity	34/100 (34) [†]	12/37 (32) [¶]	34/72 (47)	9/17 (53)* [‡]	3/11 (27)	0.158
Severe cerebral injury ^ψ	8/100 (8)	3/37 (8) [¶]	9/72 (13)	3/17 (18)* [‡]	0/11 (0)	0.141
Postnatal TAPS	35/43 (81)	2/14 (14)*	19/27 (70)	8/9 (89)	-	<0.001
BT/PET at birth for TAPS ^ψ	45/99 (46) [‡]	4/36 (11)* [¥]	33/68 (49) [£]	8/17 (47) [‡]	0/10 (0) [◇]	0.011

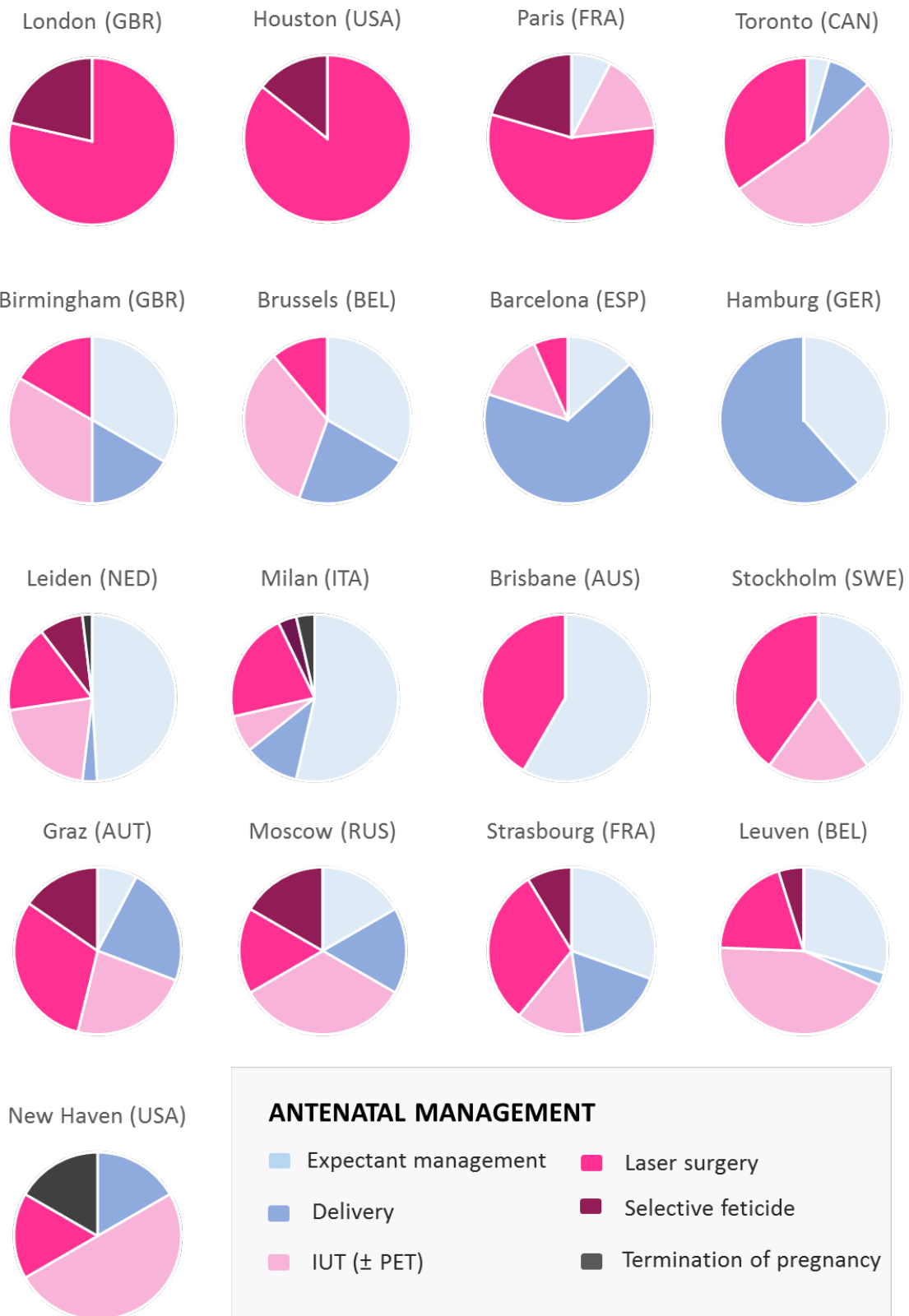
Data are presented as median (IQR) or n/N (%). To compare treatments, expectant management was set as a reference. Bold numbers represent significant p-values, an * represents the smallest p-value that is presented in the p-value column

[†] 5 missing values (2 infants died directly after birth, 3 infants with missing outcomes) [‡] 6 missing values (same as '+', plus one case with missing BT/PET information) [§] 1 missing value (unknown outcome) [¶] 2 missing values, [¥] 3 missing values (same as '¶' plus one case with missing BT/PET information) [£] 4 missing values (4 neonates unknown BT/PET information). [‡] 1 missing values (1 infant died directly after birth) , [◇] 1 missing value

IUT, intrauterine transfusion; GA, gestational age; BT, blood transfusion; PET, partial exchange transfusion; TAPS, twin anemia polycythemia sequence

^ψ Statistical correction for non-occurring events is applied

Figure 1. Antenatal management for TAPS in 17 fetal therapy centers



Appendix 1.

Center	Country	Antenatally diagnosed TAPS Cases
Leiden University Medical Center	The Netherlands	105
Leuven University Hospital	Belgium	41
Necker-Enfants Malades Hospital Paris	France	39
Children's Hospital V. Buzzi Milan	Italy	28
Center Medico-Chirurgical Obstetrical Strasbourg	France	23
Mount Sinai Hospital Toronto	Canada	22
Hospital Universitari Vall d'Hebron Barcelona	Spain	15
Saint George's Hospital London	United Kingdom	14
University of Texas McGovern Medical School at Houston	United States of America	14
Medical University of Graz	Austria	13
University Medical Center Hamburg-Eppendorf	Germany	13
Mater Hospital Brisbane	Australia	12
Brugmann University Hospital	Belgium	8
Birmingham Women's and Children's NHS Foundation Trust	United Kingdom	6
V.I. Kulakov National Medical Research Center of Obstetrics, Gynecology and Perinatology Moscow	Russia	6
Yale New Haven Hospital	United States of America	6
Karolinska University Hospital Stockholm	Sweden	5

