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Consensus report: faecal microbiota transfer – clinical applications and procedures

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SUMMARY

Background
Faecal microbiota transplantation or transfer (FMT) aims at replacing or reinforcing the gut microbiota of a patient with the microbiota from a healthy donor. Not many controlled or randomised studies have been published evaluating the use of FMT for other diseases than *Clostridium difficile* infection, making it difficult for clinicians to decide on a suitable indication.

Aim
To provide an expert consensus on current clinical indications, applications and methodological aspects of FMT.

Methods
Well-acknowledged experts from various countries in Europe have contributed to this article. After literature review, consensus has been achieved by repetitive circulation of the statements and the full manuscript among all authors with intermittent adaptation to comments (using a modified Delphi process). Levels of evidence and agreement were rated according to the GRADE system. Consensus was defined *a priori* as agreement by at least 75% of the authors.

Results
Key recommendations include the use of FMT in recurrent *C. difficile* infection characterised by at least two previous standard treatments without persistent cure, as well as its consideration in severe and severe-complicated *C. difficile* infection as an alternative to total colectomy in case of early failure of antimicrobial therapy. FMT in inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS) and metabolic syndrome should only be performed in research settings.

Conclusions
Faecal microbiota transplantation or transfer is a promising treatment for a variety of diseases in which the intestinal microbiota is disturbed. For indications other than *C. difficile* infection, more evidence is needed before more concrete recommendations can be made.

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INTRODUCTION

Recent advances in culture-independent sequencing and other high-throughput techniques have increased our understanding of the role of the gastrointestinal microbiota in health and disease. An increasing number of diseases are being linked to a disturbed intestinal microbiota composition, including metabolic syndrome, irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD) and extraintestinal disorders such as neuropsychiatric diseases.[1-3] As a consequence, therapeutic options are being tested which aim at restoring a disturbed microbiota towards a healthy, beneficial one. In general, moderate effects can be achieved by probiotic and prebiotic products, which increase the number of beneficial bacteria directly (probiotics) or indirectly by providing substrate for residing beneficial bacteria (prebiotics).[4-6] For more severe disturbances, however, these measures are not sufficient. Here, faecal microbiota transfer or transplantation (FMT) provides more powerful means to modify microbiota. It aims at replacing or reinforcing the gut microbiota of a patient with the microbiota from a healthy donor. As this procedure is not an actual transplantation, the term faecal microbial transfer is preferable. FMT is used for the treatment of recurrent *Clostridium difficile* infection with efficacy rates of 90% or even higher,[7-11] giving reason for hope that it might also be successful in other diseases where disturbances of the intestinal microbiota are involved.

There is an increasing demand from patients for access to FMT as a treatment for various disorders and diseases. However, not many controlled or randomised studies have been published using FMT for other indications than *C. difficile* infection, which makes it difficult for clinicians to decide on a suitable indication. The aim of this article is to provide an expert consensus on current indications and methodological aspects of FMT for clinical application and to provide recommendations on how to conduct clinical studies using FMT. We will first discuss applicable indications of FMT, which is then followed by a section on practicalities of the FMT procedure. As well-conducted clinical studies are still missing in most fields, it is important to note that most recommendations, especially in the indications section, are not evidence-based yet. In addition, country-specific legal regulations need to be considered when working with FMT. Safety issues have been specifically discussed in the sections on FMT in IBD (with or without concurrent *C. difficile*) and in the section on route of administration. We further provide information on the assessment of safety in the section on study design. For a systematic review of adverse events associated with FMT please refer to Baxter and Colville, 2016.[12]

METHODS

A literature review was performed by Robert-Jan Brummer (RB), Jutta Keller (JKe), Julian Kg (JK) and Arno Siebenhaar using PubMed and MEDLINE using search terms based on Faecal microbiota transplantation (Data S1) to identify studies that assessed the effect of FMT on various indications and/or practicalities of the FMT procedure. Based on these, the first draft of statements and comments was developed. The draft was then circulated among all co-authors for first round of editing. Next, the level of evidence was agreed upon by JK, JKe and RB applying the GRADE system.[7] Evidence levels could be either rated as high, moderate, low or not applicable (NA). For the statements on the General recommendations and considerations on clinical study design, Level of evidence was replaced with Grade of recommendation (rated with either high, moderate or low). Levels of evidence were not applicable regarding the exclusion criteria. Co-authors were then asked to state their level of agreement according to the GRADE system in a modified Delphi process.[8,9] The levels of agreement ranged from 1 to 6 (1: strongly disagree, 2: disagree with major reservation, 3: disagree with minor reservation, 4: agree with major reservation, 5: agree with minor reservation, 6: strongly agree). Authors were asked to provide comments if they disagreed with a statement (rating 3 or lower).

The answers were treated with confidentiality and only seen by JK, who did not participate in the voting. Consensus was defined a priori as agreement (rating 4 or higher) by at least 75% of the authors. Statements that achieved more than 75% but less than 90% agreement were discussed and/or adapted, and rated again in a second round. Statements that reached less than 75% consensus after the first round were omitted from the manuscript.

The voting team consisted of those with expertise in clinical gastroenterology and/or clinical microbiology with expertise in FMT.

RECOMMENDATIONS ON CLINICAL APPLICATIONS (INDICATIONS)

FMT in recurrent C. difficile infection

Key recommendations on FMT in recurrent C. difficile infection

	Level of evidence	Level of agreement
Patients with recurrent C. difficile infection with at least two previous standard treatments without persistent cure should be considered for FMT	HIGH	100%
Both standard or family/same household donors are applicable	HIGH	100%
If possible, patients should be included in a national registry	NA	100%
Faecal samples from patients before and after the treatment, if possible, as well as a donor sample, should be collected for follow-up in case of adverse events	NA	100%
So far, it is still unclear if antibiotic treatment and/or bowel cleansing before FMT is beneficial or if it could negatively affect the outcome (see also Recommendations on preparation of recipient)	NA	90%
No specific route of administration seems to be preferable regarding efficacy. However, preliminary data suggests that application by lower gastrointestinal tract may be safer (see also Recommendations on routes of administration)	LOW	90%

NA, not applicable.

Nowadays, FMT is established as a highly efficient treatment for recurrent C. difficile infection. FMT is included in the treatment guidelines for C. difficile infection provided by the European Society of Clinical Microbiology and Infectious Diseases, in which it is strongly recommended for multiple recurrent C. difficile infection unresponsive to repeated antibiotic treatment.[13]

Systematic reviews show that FMT treatment for recurrent C. difficile infection results in cure rates of about 90%.[8, 9, 14–16] So far, the method appears to be safe and acceptable to the patients.[14–17] The microbiota changes after FMT in C. difficile infection can persist over several months. However, more studies evaluating long-term effects on the microbiota as well as investigating possible long-term adverse events are needed.[14, 18] Currently, studies are trying to identify factors determining treatment efficacy and risk of recurrence.[19]

The current literature on FMT in C. difficile infection is mostly based on case reports, case studies and a number of retrospective studies.[15] A randomised clinical trial comparing FMT for treatment of C. difficile infection to the use of vancomycin alone and to vancomycin plus bowel lavage was stopped after an interim analysis, as FMT proved to be much more effective.[20] 13 of 16 patients (81%) achieved resolution of C. difficile infection after FMT via a nasoduodenal tube, and two of the remaining three achieved resolution after a second infusion, resulting in an overall success rate of 94%. In the patients treated with vancomycin alone, four of 13 were cured (31%), and when receiving vancomycin in combination with bowel lavage, three of 13 (23%) achieved resolution of C. difficile infection.[20] A recent double-blinded, placebo-controlled clinical study found that the administration of stool from a donor was more efficient than the administration from the patient's own stool in achieving resolution (91% vs. 63%) in C. difficile patients (FMT administered by colonoscopy).[21]

As the efficacy of FMT in C. difficile infection is widely accepted nowadays, patients do not necessarily need to be included in clinical studies. It is advisable though to include them in a registry and to accurately report adverse events. If possible, faecal samples from the patient taken before and after treatment, as well as a donor sample, should be stored to allow follow-up in case of adverse events. As such, the American Gastroenterological Association (AGA) Fecal Microbiota Transplantation National Registry from the AGA Center for Gut Microbiome Research and Education in the USA will be launched in the beginning of 2017. Its aim is to follow-up both short-term as well as long-term adverse events and safety concerns. A similar registry is already available in Germany under the name MicroTrans Registry.[22]

To avoid the potential risks associated with FMT, more selective applications of particular forms of microbes are investigated as potential alternative treatments for FMT in C. difficile. Preliminary results showed that the oral intake of nontoxigenic C. difficile spores could reduce C. difficile recurrence.[23] In addition, stool treated with ethanol to eliminate pathogens and to obtain a purified fraction of spores was shown to be effective in preventing C. difficile recurrence.[24]

FMT in severe and severe-complicated C. difficile infection

Key recommendations on FMT in severe and severe-complicated C. difficile infection

	Level of evidence	Level of agreement
FMT in severe and severe-complicated C. difficile infection should be considered as an alternative to surgery with total colectomy in case of early failure of antimicrobial therapy	MODERATE	100%
FMT could be considered already after one treatment failure	MODERATE	80%

Increasing clinical challenges in the treatment of C. difficile infection are severe courses with a considerable mortality and recurrence of the infection after successful antibiotic treatment. Different definitions of severe C. difficile infection are used, and some authors distinguish fulminant C. difficile infection or severe-complicated C. difficile infection from severe C. difficile infection as the most serious form of this infection.[13, 25, 26] If antibiotic therapy fails in severe C. difficile infection emergency total colectomy may be required. Mortality in this situation is very high and varies between 10% and 80%, mainly depending on the point of time in the course of disease when surgery is performed.[26, 27]

Besides a number of case reports[28, 29] smaller, retrospective, uncontrolled studies have been published showing that FMT is also effective in treating C. difficile infection in this clinical situation.[30–32] The cure rate was 66–88% with a single FMT and 89–94% if FMT was repeated in these patients.[30–32] Patients with severe-complicated C. difficile infection seem to have a lower primary response rate to FMT compared to severe C. difficile infection.[30, 32] FMT was applied by different administration routes, however, colonoscopic FMT was used most commonly. Some authors continued antimicrobial therapy against C. difficile infection with vancomycin during and after FMT in this patient group.[32] A recent report suggests that FMT might be used earlier in patients with the risk of a severe course. During a ribotype O27 (a C. difficile strain associated to a more severe disease course) outbreak in France, the treating physicians changed their treatment algorithm from use of FMT after at least three relapses to FMT application in addition to antimicrobial therapy during the first C. difficile infection episode. Mortality of the patients dropped from 64% to 19% with the use of the early FMT treatment approach.[33]

FMT in inflammatory bowel diseases (IBD)

Key recommendations on FMT in IBD

	Level of evidence	Level of agreement
FMT in IBD should only be performed in a research setting	NA	100%
If patients with a severely compromised colon are considered for FMT, FMT should be performed with caution as the risk for side effects is higher and systematic studies in severe disease are lacking	LOW	100%
Repeated transfers (possibly via enemas or capsules) over a longer time period seem to be preferable	LOW	90%
Possible donor variations should be considered	MODERATE	100%
Regarding efficacy, no evidence for a preferable route is available for the first administration; it should be chosen according to the location of the disease and/or the expertise of the physician. However, preliminary data suggests that application by lower gastrointestinal tract may be safer (see also Recommendations on routes of administration). For repeated administrations, enemas are recommended.	LOW	90%

There is increasing evidence that the intestinal microbiota play a key role in the aetiopathology of IBD[34, 35] IBD mouse models do not develop IBD when kept germ-free, and both an abnormal, excessive reaction to the commensal gut microbiota or components thereof, or the presence of one or several pathogens in the intestinal microbiota evoking an immune reaction are discussed as possible pathophysiologic mechanisms in IBD.

The intestinal microbiota composition has been shown to be different in both ulcerative colitis (UC) and Crohn's disease (CD), and is generally characterised by a lower diversity and a decreased stability compared to healthy controls, which may lead to the loss of normal, regulatory immune effects of the microbiota.[34, 36, 37] It is

still unclear if alterations in microbiota composition are a cause or consequence of the ongoing inflammatory processes, or a combination of both[38].

1;m|;u P&" Q ruo^b7;7 1-v;v |u;-|;7 u;|uovr;1|b^;t‹ 0;|‰;;m
ruovr;1|b^;t‹ =uol '••" |o '••–: ;ubr-u|†l 0too7 tovv ‰-v ;v|bl-
0‹ ‰;b]_bm] -m7 l;-v†ubm] o= ^ot†l;: -u|b1br-m|v ‰;u;]uo†r
above or below the 75th percentile (>3500 ml) and the 90th percentile (>5500 ml).
Results: t-1;m|- r;u1u;|- ‰-v =o†m7 bm "vw o= 1-v;v: l;t7b-m 0to
(range: 150-20 000 ml). Unplanned hysterectomy was associated with an increased risk of blood loss >3500 ml when compared with planned hysterectomy (adjusted OR [aOR] 3.7 [1.5-9.4], p = 0.01). Focal resection was associated with blood loss comparable to that of planned hysterectomy (crude OR 0.7 [0.2–2.1], p = 0.49). Blood loss >3500 ml was less common in patients undergoing successful conservative manage-
l;m| Prt-1;m|- t;=| bm vb|† :7 p = 0.02) but was more common in
r-|b;m|v ‰_o u;tt†bu;7 7;t-‹;7 _‹v|;u;1|o"S P•:••Q": R•:Kb-t
occlusion methods (uterine or iliac artery ligation, embolization or intravascular bal-
toomvQ7 -rrtb1-|bom o= †|;uo|omb1 l;7b1-|bom ou |u-m;Š-lb
;==;1| om 0too7 tovv »'"•• lt: -|b;m|v 7;tb^;u;7 0‹ v†u];omv
" ‰;u; lou; tbh;t‹ |o ;Šr;ub;m1; 0too7 tovv u: "S P (p = 0.01)
Conclusions: m ru;]m-m| ‰ol;m ‰b|_ "7 |_; tbh;tb_oo7 o= 0too7
reduced in planned vs unplanned cesarean delivery, and when the surgery was per
=oul;7 0‹ - vr;1b-tbv| ;Šr;ub;m1;7 bm |_; l-m-];l;m| o=- ": $_b
1;vvb|‹ o= 7;tb^;u‹ 0‹ -m ;Šr;u| |;-l: omv;u^-|b^; l-m-];l;m| %
with less blood loss, but only if successful. Therefore, careful patient selection is of great importance. Our study showed no consistent benefit of other adjunct measures
v†1_ -v -u|;ub-t o11t†vbom |;1_mbt†;v7 †|;uo|omb1v ou |u-m

+) ! "
abnormally invasive placenta, cesarean, high-risk pregnancy, hysterectomy, placenta, postpartum hemorrhage, uterine scar

•J|J $! & $

t|_o†]_ l-|;um-t lou|-tb|‹ u-|;v -u; 7;1tbmbm] |_; bm1u;-vbm] bm1b-dence of cesarean delivery (CD) has resulted in an increase in placenta -11u;|- vr;1|u†l P "Q7 ou -0moul-tt‹ bm^-vb^ rt-1;m|-7 -7^;uv;t‹ impacting maternal outcomes globally.[1,2] " 7;v1ub0;v |_; 1 bmb1-t disease spectrum in which a placenta does not separate spontaneously at delivery and cannot be removed without causing abnormal and potentially life-threatening bleeding due to varying degrees of placental invasion into or through the myometrium.[3,4] t|_o†]_ v|btt u;t-|b^;t‹ u-u;7 " 1-uub;v - 7bvruorou|bom-|;t‹ _b]_ ub-v; bm l-|;um-t morbidity and mortality, and contributes considerably to the proportion of postpartum hemorrhage with hysterectomy.[5] o| omt‹ bv a heterogeneous disease spectrum, but management of pregnancies ‰b|_ " ^-ub;v ‰b7;t‹ -1uovv 1;m|;uv: -m-];l;m| or|bomv bm-clude delivery by planned cesarean hysterectomy, focal myometrial resection and conservative management leaving the placenta in situ after delivery, with or without adjunctive measures such as arterial embolization or planned delayed hysterectomy.[u]

Various efforts have been made to identify associations between clinical management and maternal blood loss, morbidity and

lou|-tb|‹ ‰b|_ "7 |_;u; ‰;u; -t‹ 1om7†1|;7 0‹ vb limited data and generalizability to guide the optimal management of this condition. In an attempt to address these problems, interna-|bom-t]uo†rv7 bm1t†7bm] |_; m|;um-|bom-t "Q -m7 |_; m|;um-|bom-t Federation of Gynaecology and Obstetrics (FIGO), have published proposals for standardization of imaging[•7v] "J" _-v joined together specifically to pool international multi-center data to identify outcomes across various centers and identify research gaps.

We aimed to determine which epidemiologic factors and which l-m-];l;m| =-1|ouv ‰;u; -vvo1b-|;7 ‰b|_ _b]_ -m7 _b]_ r;ubr-u|†l 0too7 tovv bm 1olrtb1-|;7 0‹ ":

Key message

t-mm;7 ruo1;7†u;v7 bm1t†7bm] _‹v|;u;1|ol‹ -u;v;1|bom =ou rt-1;m|- -11u;|- vr;1|u†l P "Q7 ated with lower blood loss than unplanned hysterectomies.

;ubr-u|†l 0too7 tovv bv t;vv ‰_;m 1 v-u;-m 7l-m-];7 0‹ - v†u];om ou v†u]b1-t |;-l vr 1b-tbŒ;

‘J|J $! $ "

‘:•J|J -|b;m| u;1u†b|l;m|

$_; "J' 7-|-0-v; 1om|-bmv 0o|_ u;|uovr;1-|b^;t‹ tively collected obstetric and surgical data of pregnant patients >14];v|-|bom-t ‰;;hv ‰b|_ v†vr;1|;7 -m7 Fou r-|_o-]bv-tt‹ -v;v =uol rubt ‘••v |o ;1;l0;u ‘••’ ‰;u;-u;]bv|;u;7 spectively in the database. Cases from 2014 to 2019 were collected prospectively. In total, 442 cases were included in the database.[9]

‘:‘J|J Š1t†vbom 1ub|;ub-

= |_; “““ 1-v;v bm "|_7;-|-0-v;7 '‘ 1-v;v o= ‰o lom;m ‰b|_ moul-t rt-1;m|-|bom P-m|;m-|-tt‹ v†vr;1|;7 1;m|-t v;r-u-|bom7 b; >=-tv; rovb|b^; 1-v;v?Q ‰;u; ;Š1t†7;7 -m-t‹vbv: =†u|_;u ‘u 1-v;v mo| 7;tb^;u;7 0‹ N uv;-jm7 ‹rt1;m‹|- ru;^b- [n = 17] and termination of pregnancy [n · –SQ ‰;u; ;Š1t†7;7: N_mbu|m-J|-t om; 1-v;v ‰;u; ;Š1t†7;7 7†; |o lbvvbm] bm=oul-|bom om or;u-|b^; management and 15 cases due to missing data on blood loss. In total, ’’v 1-v;v ‰;u; bm1t†7;7 -m7 -m-t‹Œ;7 P b]†u;•Q:

‘:’J|J ;-v†u;l;m| o= 0too7 tovv -m7 1tbmb1-t classification of PAS

Each center recorded blood loss using their own standardized local ruo|o1ot7 ‰_;|_;u 0‹ t†-m|b=b;7 l;-v†u;l;m| ou =b;7 $_; 7;]u;; o= bm^-vbom ‰-v 1t-vvb=b;7 u-v-m7 system[7] originally proposed in 2015 and upon which the more

&! •J";t;1|bom o= 1-v;v: 7 1;v-u;-m 7;tb^;u‹ 8 placenta accreta spectrum

recently published FIGO Clinical Classification system was based.[v7••] The publication by Braun et al includes further details.[9]

‘:“J|J r|-o-v;1tt;1|bom

Data were collected both retrospectively (cases managed from •‘v|o ‘••’ -m7 ruovr;1|b^;t‹ P•‘••’•“K_-u| u;^b;‰ †v a standardized, secured and password-protected online data collection platform (FetView, Zeitgeist Health SE).[9] -u|b1br-m|v ‰;u; grouped based on blood loss in this study above the 75th percentile of our cohort (>3500 ml) and blood loss above the 90th percentile P»""•• ltQ P rr;m7bŠ "•Q:

The following factors were investigated with regard to their association with peripartum blood loss:

" ‰b|_ moul-t rt-
- Number of previous CD uol |_bv
- Pv^ ;jrm;-o=7;1t-u‹|- ru;^b-
- $_b|m-J|-t " 7b-]movbv P-m|;m-|-tt‹ v†vr;1|;7 ^v om ou ;u-|b^;
- N "J "]u-7;v o= bm^-vbom ‘K
- Degree of urgency of delivery
- N Šr;ub;m1; o= |_; v†u];om9 vr;1b-tbv| bm " ^v ‰;u;-u;‰o|v ‰b|_ vb]mb=b1-m| ;Šr;ub;m1; bm " knowledge and/or skills relating to the condition)[11]
- Operative management
  - Type of management (planned hysterectomy, unplanned hysterectomy, focal resection, placenta left in situ with uncomplicated resorption, placenta in situ followed by planned or unplanned delayed hysterectomy)
  - K ovb|bom o= |_; †|;ubm; bm1bvbom P=†m7-t transverse above placenta)
- Measures to support uterine contraction/aid blood clotting
  - K Š‹|o1bm Pruor_‹t-1|b1 -7lbmbv|u-|bom -K;7 blood loss occurred; therapeutic administration – after increased blood loss occurred)
  - K $u-m;Š-lb1 -1b7 P$* 8 ruor_‹t-1|b1 =7lbmbv| increased blood loss occurred; therapeutic administration – after increased blood loss occurred)
  - K uov|-]t-m7/E2/E1 (prophylactic administration – before increased blood loss occurred; therapeutic administration – after increased blood loss occurred)
  - Intrauterine balloon (prophylactic administration – before increased blood loss occurred; therapeutic administration – after increased blood loss occurred)
- N ;ubor;u-|b^; o11t†vbom o= †|;ubm; 0too7 v†rrt‹ occlusion reported):
  - K ;t^b1 -u|;ub-t ;l0otbŒ-|bom
  - Intravascular balloon (femoral or iliac)
  - Uterine artery ligation
  - Internal iliac artery ligation

':"J|J "|-|bv|b1-t -m-t‹v;v

Univariate and multivariate analyses were used to test associations ‰b|_ 0too7 tovv »'"•• -m7 »""•• lt: l†t|bt;ˆ;t model served to control for possible variation between participat- bm] 1;m|;uv P"•Qm 7šb_Š •" 1;m|;uv ‰;u; 7;=b om7 t;ˆ;t ˆ-ub-0t;: v - =buv| v|;r7 |_; bm=t†; loss was calculated for each first level variable separately (univariate analysis). In analyses comparing planned management approaches, planned hysterectomy was the reference category for operative management, as this is the most commonly used, definitive immediate treatment of placenta accreta spectrum.[12] Crude odds ratios P1 !Q ‰b|_ –"w 1om=b7;m1; bm|;uˆ-t P–"w u;v†t|v: ;Š|7 - l†t|bˆ-ub-|; u;]u;vvbom -m-t‹ cluding variables that had been identified as having a significant effect in univariate analysis (p ½•:•"Q: †t|bˆ-ub-|; -m-t‹v -7f†v|;7 o77v u-|bov P- !Q ‰b|_ –"w :

':uJ|J |_b1-t -rruoˆ-t

o1-t |_b1-t ollb||;;F ! -rruoˆ-t -m7 -|- &v were obtained according to local policies. Details of these can be found in the online Supporting Information contained in the second Commentary of this supplement.[9]

'J|J ! "& $"

':•J|J ;lo]u-r_b17 1tbmb1-t -m7 o†|1o characteristics of enrolled women

$-0t; v_o‰v |_; 7;lo]u-r_b1 7-|- o= |_; -m-t‹ r;u1u;|- P "]u-7; ‰-v ru;v;m| bm "vw o= 1-v l;7b-m 0too7 tovv ‰-v '••• lt P• -m7 •b]K Q: ;ubor;u-|bˆ; o11t†vbom o= †|;ubm; 0too7 v P–"F''vQ o= 1-v;v: lom] |_;v; 1-v;v7 b| ‰-v bm "uw P""F–"Q o= 1-v;v7 |_-| bv7 -=|;u o11t† The most commonly used prophylactic intervention was intravas- 1†t-u 0-ttoom rt-1;l;m| P"vF''v8 •"wQ: ˆ;u-tt7 blood loss was seen over time (Figure 2B).

':'J|J -1|ouv mo| vb]mb=b1-m|t‹ -vvo peripartum blood loss

Tables 2 and 3 show the results of the multilevel logistic regression analyses. Blood loss >3500 ml or >5500 ml did not differ between centers (inter-center variance 1.3 [0.3–4.9], p = 0.15). The number of previous CD, the presence of placenta previa and antenatal diag movbv o= " v_o‰;7 mo -vvo1b-|bom ‰b|_ No difference in blood loss was noted between focal resection and rt-mm;7 _‹v|;u;1|ol‹: o1-t u;v;1|bom ‰-v r;u

|_u;; |bl;v bm "]u-7; '7 |‰o |bl;v bm "]u-7; "]u-7; "7 om; |bl; bm "]u-7; "7 |‰o |bl;v bm

Univariate analyses did not yield significant correlations between measures to promote uterine contraction (administration of uterotonics, intrauterine balloon) or blood loss >3500 ml. No difference in blood loss was seen with prophylactic †v; o= $* P†mb-ˆ-ub-|; ml: cOR 0.5 [0.2–1.2], p = 0.12; >5500 ml: cOR 0.3 [0.1–1.5], p · •:•"8 ruor_‹t-1|b1 $*'Š Rmom$* •S': tooo7 loss >5500 ml was not significantly associated with type or timing of v†u]b1-t bm|;uˆ;m|bom PuoS!7 •:"•vR*o-uK †mrt-mm;7 _‹v |;u;1|ol‹8 - ! •:–u R'6*7K p = 0.92 for delayed hysterectomy). Univariate analyses showed increased association between cases with blood loss >3500 and blood loss >5500 ml in emergent CD vs scheduled CD (cOR 3.5 [1.2–10.2], p = •:•' -m7 1 ! ':uu R•S•7K p = 0.04, respectively), but not after multivariate analysis. Univariate analyses did not yield significant correlations between perioperative occlusion of uterine blood supply available in our dataset (uterine artery embolization, femoral balloon, uterine artery ligation, internal iliac artery ligation) and blood loss >3500 or >5500 ml.

':'J|J -1|ouv -vvo1b-|;7 ‰b|_ vb]mb=b1-m increased risk for high peripartum blood loss

Compared with planned hysterectomy, unplanned hysterectomy was associated with significantly higher odds of blood loss >3500 ml (aOR 3.7 [1.5–9.4], p = 0.01). The association with blood loss »""•• lt 7b7 mo| _ot7 bm l†t|bˆ-ub-|; -m-t‹v P- p · •:•vQ: ;t-‹;7 _‹v|;u;1|ol‹ ‰-v -vvo1b-|;7 ‰b|_ - |_;]_;u tbh;tb_oo7 o= |o|-t 0too7 tovv '»'"•7 lt P- p · •:•••Q: t-1;m|- r;u1u;|- ‰b|_ r-u-l;|ub-t bmˆ- showed a trend to a higher proportion of cases with blood loss >3500 ml (aOR 3.4 [0.9–12.3], p · •:•uQ7 ‰b|_ bmvb]mb=b1-m b-mv;|u-t vu-t7 0too7 tovv »""•• lt PS7 p = 0.32). There was a positive correlation between therapeutic internal iliac artery tb]-|bom -m7 0too7 tovv »'"•• lt PS7 p = 0.03). R•:'K Manual removal of placenta was attempted significantly less fre- u;m1; o= |_; 0too7 tovv »'"•• lt]uo†r -m7 om to‰;u "]u-7;v o= bmˆ-vbom P]u-7;v •:uS7 '8 - p = 0.01).

':"J|J -1|ouv -vvo1b-|;7 ‰b|_ vb]mb=b1-m risk for high peripartum blood loss

Interestingly, fewer cases with blood loss >3500 ml occurred for placenta percreta grade 4 in multivariate analysis (aOR 0.4 [0.1–0.9]; p · •:•"7 u;=;u;m1; 1-|;]ou‹9 "]u-7; o= bmˆ- ‰-v lou; ruomo†m1;7 =ou 0too7 tovv »"•'•S7t P- ! p = 0.01). Leaving the placenta in situ was associated with fewer cases of blood loss >3500 ml but only if it was successful without =†u|_;u bm|;uˆ;m|bom PS = 0.02). Delivery by a sur];om ;Š r;u;m1;7 bm " ‰-v v|uom]t‹ u;t-|;7 |o 0

[illegible] not shown as it denotes normal placentation. 3500 ml (75th percentile) and 5500 ml (90th percentile) are marked to illustrate the thresholds used to compare cases with high peripartum blood loss

[illegible] = 0.003, respectively).

[illegible]

[illegible] most common treatment method used within our multi- center international cohort.[12,13] Conservative management, whether by leaving the placenta in situ or via partial myometrial resection has been shown to be feasible, with favorable short-term maternal outcomes [illegible] To date, it is unclear whether conservative approaches confer a significant reduction in peripartum blood loss. Within this cohort, leaving the placenta in situ was associated with lower odds of blood loss >3500 ml compared with planned cesarean hysterectomy when successful [illegible] n = 24). When [illegible] n = 15, including planned and unplanned), it was associated with higher [illegible] leaving the placenta in situ confers risks of secondary postpartum hemorrhage, sepsis or disseminated intravascular coagulation.[15-17]

[illegible][14] [illegible] it seems possible that specific hemostasis over pedicles that irrigate the placenta and the invaded area can help to reduce blood loss >3500 ml.

Interestingly, the odds for blood loss >3500 ml were similar between focal resection and planned hysterectomy. This suggests that focal resection is a feasible option for women who want to keep their uterus, when the location and size of placental invasion permits this procedure.

There was no significant association of blood loss >3500 and >5500 ml and the use of adjunctive measures to reduce blood loss, [illegible] [1.4–4.2; p = 0.001). This positive correlation likely reflects the indication of ongoing bleeding rather than a failure of efficacy. Overall, the prophylactic use of adjunctive measures was relatively infre- [illegible] One recently published [illegible] the grade of invasiveness) was effective in significantly reducing the intraoperative blood loss compared with the placebo group.[19] Well-designed and appropriately powered studies to address the safety and efficacy of adjunctive measures are essential to understand their utility. Newer studies suggest that arterial occlusion of the [illegible][20,21] In a recent randomized controlled trial that included 100 women with placenta previa and [illegible] iliac artery balloon occlusion did not reduce the number of units of packed red blood cells transfused or otherwise improve outcomes.[22]

Even placenta accreta or increta (lower grades) can be associated with blood loss >3500 and >5500 ml. Conversely, in placenta per- [illegible] in cases involving placental invasion into other organs, whereas placenta percreta without invasion of other organs was associated [illegible] be easily detected both on antenatal ultrasound as well as intraoperatively, so that manual removal of the placenta was not attempted, [illegible] ageable. Lesser degrees of invasion may permit partial placental separation and bleeding from the placental bed or greater willingness [illegible]