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Gender differences in outcomes of arteriovenous fistulas in hemodialysis patients

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Gender differences in outcomes of arteriovenous fistulas in hemodialysis patients.

Background. The prevalence of arteriovenous (A-V) fistula use is lower among female than male hemodialysis patients. This difference may be due, in part, to smaller vessel diameter in women. However, even when routine preoperative vascular mapping is used to select vessels with suitable diameters, fistulas are still less likely to mature in women than in men.

Methods. To explore the reasons for this gender discrepancy, we evaluated the outcomes of 230 A-V fistulas placed at our institution after preoperative mapping. Vessel diameters, radiologic and surgical interventions, and fistula adequacy for dialysis were assessed.

Results. Fistula adequacy for dialysis was lower in women than men (31 vs. 51%, $P = 0.001$). The inferior outcome of fistulas in women was observed for both forearm fistulas (18 vs. 43%, $P = 0.02$) and upper arm fistulas (39 vs. 60%, $P = 0.04$). Differences in vessel diameter did not explain the lower patency rate of fistulas among women. Among fistulas not lost due to technical failure or early thrombosis, 31% underwent one or more interventions (salvage procedures) due to failure to mature. These interventions included angioplasty, ligation of tributaries, superficialization, and surgical revision of the anastomosis. A salvage procedure was more likely in women than in men (42 vs. 23%, $P = 0.04$). The likelihood of fistula maturation after an intervention was similar among women and men (50 vs. 37%, $P = 0.40$). Salvage procedures increased the proportion of adequate fistulas to a greater degree in women than in men (relative increases of 68 and 15%, respectively).

Conclusions. These data suggest that fistulas are less likely to be useable for dialysis in women than in men, despite routine preoperative mapping and frequent interventions undertaken to salvage immature fistulas.

The National Kidney Foundation Kidney/Dialysis Outcomes Quality Initiative (NKF-K/DOQI) guidelines recommend increasing placement of arteriovenous fistulas in patients with end-stage renal disease (ESRD) [1]. Numerous studies have reported a lower prevalence of fistula use in women than in men [2–8], but the reasons for this discrepancy have not been adequately elucidated. One possible explanation is that vessels are of smaller caliber in women than in men, and therefore less likely to dilate sufficiently to sustain a blood flow adequate for hemodialysis. This hypothesis is supported by our recent finding that women were significantly less likely to have suitable vessels for construction of a fistula, when objective preoperative sonographic criteria were used [9]. However, the likelihood of successful maturation of fistulas placed after preoperative vascular mapping was still lower in women than men, suggesting additional factors adversely affecting fistula outcomes [9].

To be used successfully for dialysis, a new fistula must meet several conditions. First, the draining vein must dilate adequately to permit frequent cannulation. Second, the blood flow through the fistula must be high enough to enable a dialysis blood flow of ≥350 mL/min. Finally, the fistula must be sufficiently superficial to allow appreciation of the anatomic landmarks and safe cannulation. Specific radiologic or surgical interventions can convert an immature fistula to one that can be used successfully for dialysis. Stenosis at the arteriovenous anastomosis or in the draining vein can be corrected by surgical revision or angioplasty [9–11]. Large tributary veins can be ligated to promote increased blood flow through the main draining vein [9, 10, 12]. A fistula that is too deep can be superficialized by dissecting it out and tunneling it in the subcutaneous tissue [9, 13–15]. Two recent investigations [10, 11] reported a high success rate in salvaging immature fistulas with radiologic interventions. However, it is not known whether the frequency of such interventions, or their success, differ among women and men.

To further understand the inferior outcomes of fistulas in women, we compared the early outcomes of A-V fistulas in female and male patients who had their procedure performed at our institution with the benefit of preoperative vascular mapping.

Key words: vessel diameter, cannulation, dialysis blood flow, stenosis, angioplasty, preoperative vascular mapping.

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METHODS

Fistula placement

All patients requiring placement of a vascular access were referred to one of three transplant surgeons with experience in the procedure. Preoperative sonographic vascular mapping was obtained in over 90% of cases, and was used by the surgeons to select the optimal vascular access for each patient, according to criteria agreed upon in advance by the nephrologists, surgeons, and radiologists [16]. Briefly, the minimum vessel diameter required was 2.5 mm for the vein (with a tourniquet) and 2 mm for the artery. Moreover, the draining vein had to be free of stenosis or thrombosis up to the medial subclavian vein, and without indirect evidence for central venous abnormality. The preferred type of A-V fistula was a forearm radiocephalic fistula, followed by an upper arm brachiocephalic fistula, followed by a brachiobasilic transposition fistula. The fistula was constructed by suturing the end of the vein to the side of the artery. An A-V graft was reserved for patients with no suitable vasculature for any type of fistula. Among patients receiving their first vascular access, only 26% received a graft because preoperative mapping findings precluded fistula placement. The vast majority of fistulas were placed as an outpatient procedure.

Postoperative fistula management

New fistulas were monitored by the dialysis nurses after their placement, but were not generally used until eight weeks after their placement (due to prior institutional experience with difficulties in cannulation, infiltration, and thrombosis in fistulas used less than 8 weeks after placement). In addition, a postoperative ultrasound (~6 weeks after fistula creation) was obtained in some patients to assess the vein diameter, access blood flow, and depth of the fistula from the skin [17]. Patients whose fistulas were deemed immature at six to eight weeks by clinical or sonographic criteria were referred for salvage procedures. These included angioplasty of a stenosis in a draining vein, ligation of large tributary veins, superficialization of the draining vein, or surgical revision of the arteriovenous anastomosis.

Data analysis

Using a prospective, computerized database of all vascular access procedures performed at the University of Alabama of Birmingham (UAB) medical center [18], we identified all patients who had a new arteriovenous fistula placed for hemodialysis during the two-year period from 1/1/99 to 12/31/00. We obtained approval from the local Institutional Review Board to review the patients' medical records for research purposes. Fistula outcomes were defined prospectively. A "technical failure" occurred when the vessels were deemed by the surgeon during the exploration to be unsuitable for fistula creation or when the fistula was constructed but clotted within 24 hours. "Early thrombosis" was defined as clotting of the fistula (by clinical evaluation) within eight weeks of its placement (prior to attempting cannulation). "Failure to mature" was defined as inability to achieve adequacy for dialysis within six months of placement, in the absence of technical failure or early thrombosis. A fistula was deemed "adequate for dialysis" if it was used for at least one month and achieved a dialysis blood flow $\geq$350 mL/min on at least six dialysis sessions [19]. If the fistula was placed in a pre-dialysis patient, its adequacy was determined after initiation of maintenance hemodialysis. The outcome of a fistula was "indeterminate" if (*1*) the patient had not yet started dialysis at the time of data analysis (9/30/01), or (*2*) the patient died, received a kidney transplant, was transferred to a non-participating dialysis unit, or switched to peritoneal dialysis before fistula adequacy could be assessed.

We also evaluated whether differences in vascular diameter may contribute to differences in the success rate of fistulas between women and men. Initially, we compared the diameters of the artery and vein at the anastomotic site between the genders. Because we had previously observed a difference between the outcomes of upper arm and forearm fistulas [19], separate comparisons were performed for fistulas at the two anatomic locations. Subsequently, the vascular diameters of fistulas that were successful were compared with those of fistulas that failed to achieve adequacy for dialysis.

Statistical analysis

The differences in fistula outcomes among patient subsets were analyzed using the χ^2. Mean vascular diameters between patient subgroups were compared by the Student *t* test. In addition, receiver operator characteristic (ROC) curves were generated to explore the relationship between the initial adequacy of fistulas for dialysis and the preoperative arterial and venous diameters. A P value <0.05 was considered statistically significant.

RESULTS

During the two-year period from 1/1/99 to 12/31/00 a total of 249 fistulas were placed at our institution. Of those, 230 (or 92.5%) were placed with the benefit of preoperative vascular mapping. The outcomes of 41 fistulas was indeterminate due to patient death (10 patients), renal transplant (1), transfer to a non-participating dialysis unit (8), change in modality to peritoneal dialysis (2), loss of patient to follow-up (5), or because the patient had not yet started dialysis at the time of data analysis (15). The remaining patients with known fistula outcomes served as the study population. Their mean age was 54 $\pm$ 14 years (range, 17 to 80 years). Other

Table 1. Demographic and clinical characteristics of the study patients

Characteristic	*N* patients	Percent of patients
Gender		
Male	105	56
Female	84	44
Race		
Black	139	74
White	50	26
Age		
≥65 years	39	21
<65 years	150	79
Diabetes		
Yes	100	53
No	89	47
Fistula location		
Upper arm	103	54
Forearm	86	46
First access?		
Yes	130	69
No	59	31

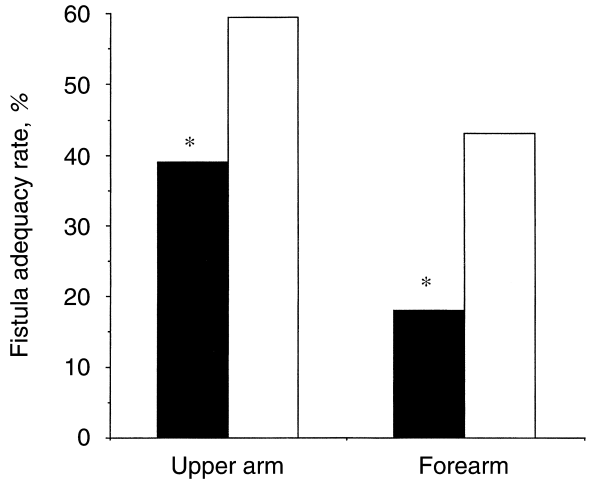

Fig. 1. Fistula adequacy for dialysis, sorted by patient gender and site of fistula. Symbols are: (■) females; (□) males; *$P < 0.05$.

Table 2. Overall fistula outcomes in males versus females

	Female	Male	All pts
Adequate	27 (32%)	53 (50.5%)	80 (42%)
Adequate without interv	16 (19%)	46 (44%)	62 (33%)
Adequate after interv	11 (13%)	7 (6.5%)	18 (9%)
Not adequate	57 (68%)	52 (49.5%)	109 (58%)
Technical failure	11 (13%)	3 (3%)	14 (7%)
Early thrombosis	21 (25%)	20 (19%)	41 (22%)
Failure to mature	25 (30%)	29 (27.5%)	54 (29%)
Total	84	105	189

$P = 0.001$ for differences in outcomes between men and women

Table 3. Preoperative vascular diameters for forearm and upper arm fistulas, sorted by patient gender

	Female	Male	*P* value
Forearm fistula			
Artery diameter	0.25 ± 0.04	0.28 ± 0.04	0.004
Vein diameter	0.29 ± 0.04	0.30 ± 0.04	0.34
Upper arm fistula			
Artery diameter	0.42 ± 0.09	0.54 ± 0.14	<0.001
Vein diameter	0.41 ± 0.11	0.41 ± 0.14	0.90

Table 4. Preoperative vascular diameters for forearm and upper arm fistulas, sorted by fistula outcome

	Adequate fistula	Inadequate fistula	*P* value
Forearm fistula			
Artery diameter	0.27 ± 0.05	0.27 ± 0.04	0.91
Vein diameter	0.30 ± 0.05	0.29 ± 0.04	0.07
Upper arm fistula			
Artery diameter	0.48 ± 0.16	0.47 ± 0.10	0.62
Vein diameter	0.42 ± 0.13	0.40 ± 0.11	0.51

demographic and clinical features of this patient population are summarized in Table 1.

Among the 189 patients with known fistula outcomes, 80 (42% of the total) were adequate for dialysis, whereas 109 (58% of the total) were inadequate. The inadequate fistulas included technical failures (7%), early thrombosis (22%), and failure to mature (29%). The overall fistula adequacy rate was about one-third lower among female than male patients ($P = 0.001$; Table 2). Moreover, the inferior outcome of fistulas in women was observed for both forearm and upper arm fistulas (Fig. 1).

As expected, both the arterial and venous diameters at the anastomotic site of the fistula were greater in upper arm, as compared with forearm fistulas (Table 3). However, the arteries used for fistula construction were significantly smaller in women than in men, whether one examined forearm or upper arm fistulas. In contrast, with the benefit of preoperative vascular mapping, the vein diameters were similar between the genders. Diabetic status and patient age were not predictive of the arterial or venous diameters (data not shown).

If the lower vascular diameters accounted for the inferior outcomes of fistulas in women as compared with men, one would expect inadequate fistulas to have smaller preoperative vascular size than those measured in fistulas that were successful for dialysis. In contrast to this expectation, both the arterial and venous diameters were similar in adequate and inadequate fistulas, and this observation was true for both upper arm and forearm fistulas (Table 4). Moreover, ROC curves relating fistula adequacy to preoperative arterial and venous diameters were similar to the line of identity (Fig. 2), suggesting that above the threshold diameters used, vascular diameter was not predictive of fistula adequacy.

Fifty-five fistulas did not achieve adequacy for dialysis due technical failures or early thrombosis. Among the remaining 134 fistulas, 41 (or 31%) underwent 55 salvage

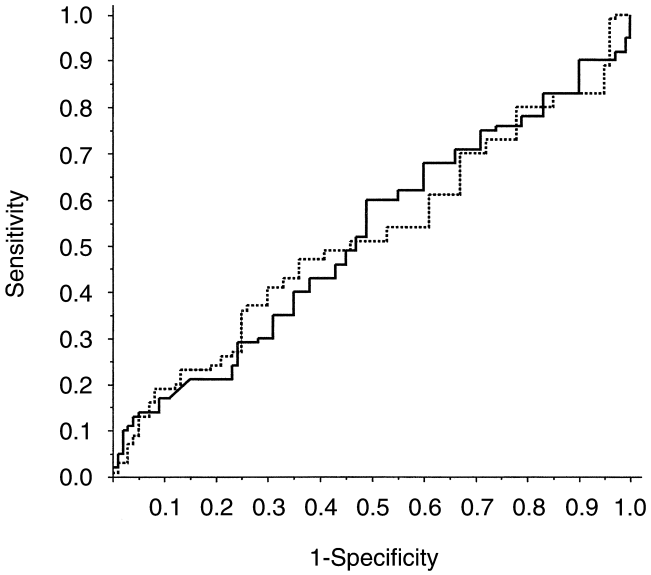

Fig. 2. Receiver operator characteristic (ROC) curves relating the initial adequacy of fistulas for dialysis to preoperative arterial diameter (solid line) and vein diameter (dotted line). An ROC curve similar to the line of identity suggests no predictive value of vascular diameter for fistula outcome.

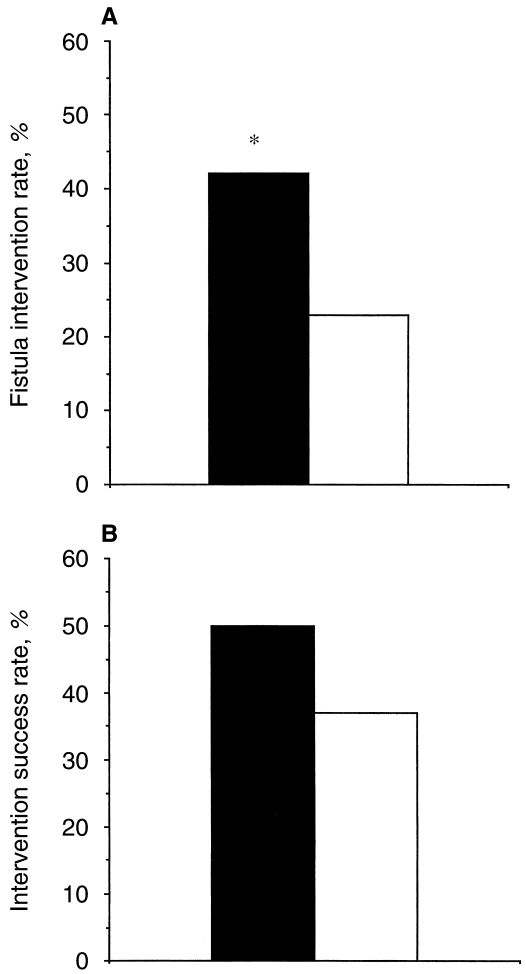

Fig. 3. (*A*) Intervention rate for immature fistulas, after exclusion of technical failures and early thrombosis. (*B*) Likelihood of fistula adequacy for dialysis after salvage procedure. Symbols are: (■) females; (□) males; $*P < 0.05$.

procedures in an attempt to promote their maturation. These included 13 angioplasties of stenosis in the draining vein, 17 ligations of tributary veins, 11 superficialization procedures for fistulas that were too deep for cannulation, and 14 surgical revisions of the anastomosis. A single salvage procedure was performed in 29 patients; 10 patients required two salvage procedures, and two patients required three procedures. Salvage procedures were performed almost twice as often among women than men (Fig. 3). The distribution of the four types of interventions differed between the genders (Table 5). A superficialization procedure accounted for 30% of the salvage procedures in women, but only 8% of those performed in men ($P = 0.04$).

The type of salvage procedure required differed substantially between forearm and upper arm fistulas ($P < 0.05$; Fig. 4). Ligation of tributary veins and surgical revision of the arteriovenous anastomosis was more commonly utilized in forearm than in upper arm fistulas. In contrast, angioplasty of a stenosis in the draining vein and a superficialization procedure was more commonly necessary in upper arm than forearm fistulas.

Following salvage procedures, 18 of 41 fistulas (44%) achieved adequacy for dialysis. The maturation rate was similar in fistulas undergoing each of the four types of salvage procedures: 54% after angioplasty, 47% after ligation of tributary veins, 64% after superficialization procedures, and 36% after surgical revision of the anastomosis ($P = 0.56$). Moreover, the success rate of salvage procedures in achieving fistula adequacy for dialysis was not significantly different between women and men (50 vs. 37%, $P = 0.40$; Fig. 3). The outcomes of individual types of salvage procedures, sorted by gender, are displayed in Table 5.

In the absence of salvage procedures the maturation rate of all fistulas placed was significantly lower in women as compared with men (Table 2). Salvage procedures increased the proportion of adequate fistulas substantially in women, from 19 to 32%; the relative increase in men was much more modest, from 44 to 50.5% (Table 2).

DISCUSSION

Because women account for almost half of all hemodialysis patients [4], increasing the prevalence of fistula use among female patients is critical, if one wants to increase the overall frequency of fistulas in the dialysis population. Whereas numerous investigators have reported that women are less likely than men to dialyze

Table 5. Type of salvage procedures and their outcomes

	Female			Male		
	N interv	*N* (%) in UA	*N* (%) successful	*N* interv	*N* (%) in UA	*N* (%) successful
Type of interv						
PTA	7	7 (100%)	5 (71%)	6	4 (67%)	2 (33%)
Trib lig	8	6 (75%)	4 (50%)	9	3 (33%)	4 (44%)
Supf	9	8 (89%)	6 (67%)	2	2 (100%)	1 (50%)
Surg rev	6	4 (67%)	1 (17%)	8	2 (25%)	4 (50%)
No of interv						
1	16	13 (81%)	8 (50%)	14	9 (64%)	4 (28%)
2 or 3	6	5 (83%)	3 (50%)	5	1 (20%)	3 (60%)

An intervention was considered successful, if the fistula subsequently achieved adequacy for dialysis. Abbreviations are: UA, upper arm; PTA, percutaneous transluminal angioplasty of stenosis in draining vein; Trib lig, ligation of venous tributaries; Supf, superficialization procedure; Surg rev, surgical revision of anastomosis.

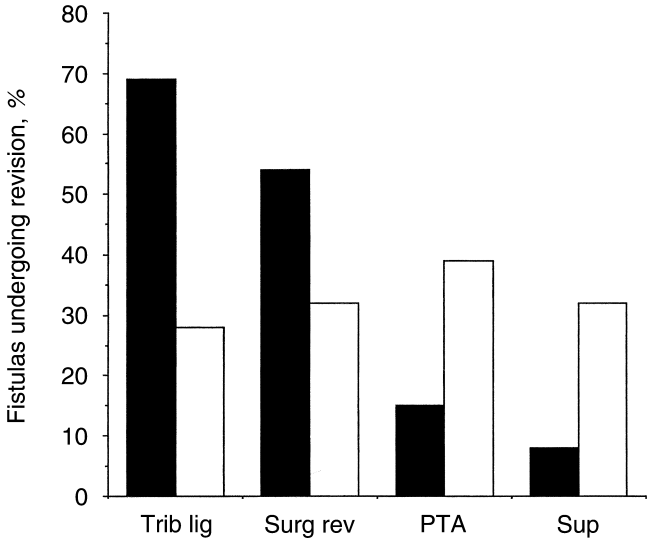

Fig. 4. Frequency of salvage procedures among fistulas undergoing a revision, sorted by type of revision and location of fistula. Symbols are: (■) forearm fistulas; (□) upper arm fistulas. Abbreviations are: Trib lig, ligation of venous tributaries; Surg rev, surgical revision of anastomosis; PTA, percutaneous transluminal angioplasty of stenosis in draining vein; Sup, superficialization procedure. Each bar represents the percent of a given intervention among all fistulas undergoing a salvage procedure. Percents add up to >100% because some patients required more than one intervention. $P < 0.05$ for comparison between forearm and upper arm fistulas.

with a fistula [2–8], few authors have tried to explain this discrepancy. One possible explanation is that female patients have smaller vessels than males, thereby decreasing the chance that a new fistula will mature adequately for dialysis. In support of this hypothesis, we observed that, in the absence of preoperative vascular mapping, forearm fistulas had a much lower success rate in women than in men (7 vs. 46%) [19]. In contrast, the success rate of upper arm fistulas was comparable between the genders (56 vs. 61%) [19]. Once we began to use routine preoperative sonographic mapping to plan vascular access placement [16], we found that women were about one-third less likely than men to have vessels of a suitable size for construction of an A-V fistula [9]. Moreover, a fistula was more likely to be placed in the upper arm, rather than the forearm, in women than in men (64 vs. 36%) [9]. In agreement, a recent multicenter study observed that an upper arm fistula was more likely to be used for dialysis in female than in male patients (43 vs. 30%) [3].

It can be argued that despite the use of preoperative vascular mapping to exclude inadequate vessels, the inferior outcomes of fistulas in women may be due to a smaller mean vessel size in women than in men. We did, in fact, find a smaller mean arterial size in women than in men, although there was no difference in vein diameter between the genders (Table 3). This difference in arterial size used for fistula construction conceivably could lead to a higher failure rate of new fistulas among women. However, the lack of difference in vessel diameter between inadequate and adequate fistulas (Table 4) argues against such an explanation.

The optimal cutoff for artery and vein diameters suitable for dialysis has not been evaluated systematically. Wong et al observed that if the artery or vein diameter was <1.5 mm, the fistula always failed to mature [20]. This finding suggests that the minimum vessel diameters should be somewhat higher. Silva et al proposed a cutoff of 2 mm for the artery and 2.5 mm for the vein, and achieved excellent fistula adequacy rates using these thresholds [21]. We have adopted the same cutoffs at our institution [9, 16]. However, analysis of the predictive value of vessel size on fistula adequacy has not been reported to date. The ROC analysis in the present study (Fig. 2) strongly suggests that higher cutoffs of artery or vein diameters used for fistula construction would not improve fistula outcomes.

The primary failure rate of upper arm fistulas in the current study (~50%) was higher than that reported in other recent published series [22, 23]. We attribute this in part to our aggressive attempts to place fistulas in any patient whose preoperative vascular mapping indicates suitable anatomy for any type of fistula. Among patients

referred for their initial vascular access, about three-fourths received a fistula rather than a graft. It is likely that these liberal selection criteria resulted in an increase of patients with marginal vessels in whom a fistula was attempted. In addition, in our previous paper, technical failures were excluded from the analysis of fistula outcomes [9]. The current study included technical failures, thus increasing the proportion of primary failures.

The current study found that the lower fistula adequacy rate in women appears to be largely due to a higher occurrence of technical failures and early thrombosis (Table 2). Moreover, even after excluding patients whose fistulas failed for one of these two reasons, a salvage procedure was required about twice as often in women than men (Fig. 3). The higher intervention rate in women was attributable, in part, to the large number of fistulas that required superficialization before they could be cannulated safely. The likelihood that an intervention resulted in fistula maturation was comparable in both genders (Fig. 3). The net effect was that salvage procedures increased the proportion of adequate fistulas to a greater degree in women (a relative increase of 68%), but only modestly in men (a relative increase of 15%; Table 2). Thus, a systematic approach to intervention in immature fistulas results in an appreciable increase in fistulas useable for dialysis. Even the 15% increase in adequate fistulas observed in men is substantial enough to warrant the use of salvage procedures in men.

Beathard, Settle and Shields recently reported on the effect of radiologic interventions on the salvage of immature fistulas [10]. Among 71 patients referred for possible intervention, eight were deemed on clinical evaluation to have insufficient arterial inflow, and were not studied further. The remaining 63 patients underwent at least one salvage procedure, including angioplasty of a stenotic lesion, ligation of tributary veins, or temporary banding of the main draining vein. Two or more interventions were required in 38% of the cases. The net result was that 82.5% of the fistulas subjected to an intervention achieved maturation, using a similar definition as in the present study. Turmel-Rodrigues et al performed angioplasty of stenotic lesions in 69 immature fistulas, and reported that 88% were patent for dialysis at three months follow-up [11]. Our success rate of salvage procedures in achieving fistula adequacy for dialysis (44%) was substantially lower than that observed in two previous reports [10, 11]. The previous two studies had a significant selection bias, as only patients referred by their nephrologists for an intervention were included. The criteria for referral were not well defined. In contrast, the present study describes the outcomes of interventions in a well-defined group of patients with clear criteria for referral and for assessment of outcomes. Moreover, the two previous studies analyzed only radiologic interventions, whereas the present series included surgical interventions. Finally, previous studies did not analyze fistula outcome by patient gender, so it is unknown whether they observed differences between men and women in the frequency of referral or likelihood that a salvage procedure resulted in fistula maturation.

In addition to optimizing selection of vessels for fistula construction, preoperative mapping may be a valuable tool in predicting which fistulas are likely to require a second procedure to achieve adequacy for dialysis. For example, in obese patients the cephalic vein is quite deep in the upper arm, such that a second superficialization procedure is commonly required before the fistula can be cannulated safely. Our observations indicate that this type of salvage procedure is required much more commonly in women than in men (Table 5). Similarly, when the preoperative sonographic assessment reveals large tributary veins, these may need to be ligated to achieve fistula maturation. Patients should be advised during their preoperative visit that a second surgical or radiologic intervention may be necessary following fistula placement to ensure that their fistula is useable for dialysis. Because forearm fistulas have a particularly low success rate in female patients, it would be desirable to identify additional preoperative sonographic markers that predict the outcome of forearm fistulas in this patient population.

In conclusion, we have found that fistula adequacy for dialysis is worse in women than in men, even when routine preoperative vascular mapping is used to guide the surgeons. Moreover, differences in vascular diameter between women and men cannot explain the inferior outcome of fistulas in women. It is not known why fistulas are more prone to technical failures and early thrombosis in women than in men. Possible explanations include differences in vascular reactivity and platelet aggregation after vascular injury or impaired ability of veins to dilate when exposed to arterial pressures. Further investigation is required to elucidate the pathophysiologic factors contributing to lower fistula adequacy rates in women, and to develop specific measures to improve these outcomes.

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