Hypothesis: Live donor adult liver transplantation (LDALT) is a safe and efficacious treatment for patients with end-stage liver disease.

Design: Case-control study.

Setting: Hepatobiliary surgery and liver transplantation unit.

Patients: From December 10, 1998, through April 10, 2000, a single team performed 15 LDALT procedures with 2 simultaneous living donor kidney transplants. During this period, 66 potential donors were screened and evaluated.

Interventions: Potential donors were evaluated with 3-dimensional helical computed tomographic scan, including volume renderings for hepatic lobar volume, vascular anatomy, virtual resection planes, and morphologic features. Suitable donors undergo complete medical and psychiatric evaluation and preoperative arteriography.

Main Outcome Measures: Donor demographics, evaluation data, operative data, hospital length of stay, and morbidity.

Results: A total of 38 men (58%) and 28 women (42%) were evaluated with 15 donors participating in LDALT. Two additional donors provided kidney grafts for simultaneous transplantation at the time of LDALT. Thirty-two donors (48%) were rejected for either donor or recipient reasons, and 10 patients (15%) elected not to participate after initial screening. Three-dimensional volume renderings by helical computed tomographic scan predicted right lobe liver volume within 92% of actual graft volume. Donor morbidity, including all complications, was 67% with no mortality. Residual liver regenerated to approximately 70% of initial volume within 1 week and 80% within 1 month after surgery.

Conclusions: Donor evaluation is an important component of LDALT. Significant donor morbidity is encountered even with careful selection. To minimize donor morbidity, groups considering initiating living donor programs should have expertise in hepatic resection and vena cava preservation using the "piggyback" technique during liver transplantation.

PATIENTS AND METHODS

DONOR AND RECIPIENT SELECTION

From December 10, 1998, to April 10, 2000, a single team performed 15 LDALT procedures and 2 simultaneous living donor kidney transplantations. Sixty-six potential donors were evaluated. Donors were between 18 and 60 years of age and shared either a genetic or significant emotional relationship with the recipient. No Good Samaritan liver donors were considered for evaluation.

All recipients being considered for LDALT were listed for cadaveric liver transplantation with the United Network for Organ Sharing (UNOS). Patients with chronic cirrhosis, liver disease and acute decompensation (UNOS status 2A) were not considered acceptable candidates for LDALT. The donor evaluation protocol followed at the Lahey Clinic Medical Center is outlined in Figure 1.

Phase 1

Figure 1A outlines phase 1 of the donor evaluation protocol. Voluntary, unsolicited contact by the donor to the transplant team initiates the evaluation process. A brief telephone interview conducted by a transplant coordinator obtains donor demographic data and documents the relationship of the donor and recipient. The potential donor is then sent a packet of information, including a description of the evaluation process and surgical procedure and a letter to present to his/her primary care physician requesting screening liver function test results and blood type verification. All potential donors with compatible blood type and normal screening laboratory values meet with a transplant surgeon to discuss the details of the surgery, postoperative care, complications, and reported outcomes associated with LDALT.

Phase 2

Figure 1B outlines phase 2 of the donor evaluation protocol. Since anatomic considerations are often the most common reason for donor rejection, our policy has been to perform a helical abdominal computed tomographic (CT) scan with 3-dimensional renderings for morphologic features, liver volume, and vascular anatomy before the medical evaluation of the donor (Figure 2). The potential recipient also undergoes CT imaging to evaluate the liver for the presence of tumor and portal vein patency. Donors with an estimated ratio of right lobe liver volume to recipient body weight of 0.8% or more are referred for complete medical and psychosocial evaluation.

The internal medicine physician and psychiatrist evaluating potential donors are completely independent of the transplant team and have no prior knowledge of the recipient's condition or interests. Laboratory tests, including complete blood cell count, liver and renal biochemistry values, thyroid function tests, coagulation profile, and serological studies for hepatitis A, B, and C and cytomegalovirus, are performed as part of the medical evaluation. Chest x-ray examination, electrocardiogram, and Doppler ultrasound of the liver are also obtained. Additional studies deemed necessary by the examining physician are obtained on a selective basis (eg, pulmonary function studies, cardiac stress test, colonoscopy, mammography) depending on the individual donor.

A multidisciplinary screening committee composed of representatives from internal medicine, transplant surgery, anesthesia, blood bank, nursing, social work, psychiatry, and ethics meets weekly to review each potential donor's candidacy. No exception is made in the donor selection protocol to accommodate the needs or interests of the recipient. Facilitated workup can be accomplished in a few days in urgent situations. The screening committee reviews all data to determine the suitability of the donor-recipient pair as candidates for LDALT. The decision of the committee is discussed with the donor first so that those potential donors who may have changed their mind during the evaluation period have the opportunity to abort the donation process. Decisions of donors to abort the donation process are kept confidential and are ascribed to medical or anatomic constraints to preserve the relationship between the donor and recipient.

Phase 3

Figure 1C outlines phase 3 of the donor evaluation protocol. The recipient is reevaluated by the transplant team and have no prior knowledge of the recipient's condition or interests. Laboratory tests, including complete blood cell count, liver and renal biochemistry values, thyroid hormone tests, coagulation profile, and serological studies are performed. Additional studies, such as mammography) depending on the individual donor.

Donor selection and exclusion criteria, anatomic findings, and surgical outcome are reviewed.

RESULTS

All data are shown as mean±SEM. Thirty-eight men (58%) and 28 women (42%) were evaluated as potential live donors. Most donors were blood group O (68%), were relatively young (38.5±2.1 years), and had normal body weight (body mass index, 26.9±0.9). Seventeen individuals provided 15 right lobe liver grafts and 2 kidney grafts to 15 recipients. In the first simultaneous liver and kidney recipient, a bilateral nephrectomy was performed as well. This patient developed end-stage renal disease from hyperoxaluria, and nephrectomy was performed to decrease oxalate load postoperatively.

Of all donors evaluated, 32 (48%) were rejected for either donor or recipient reasons. Fifteen (23%) were accepted and underwent donor right hepatectomy, and 2 additional patients were accepted as kidney donors and underwent live donor nephrectomy. Thus, 2 recipients had simultaneous kidney transplantation at the time of LDALT. Nine patients have been accepted as liver donors and are awaiting LDALT. Ten potential donors (15%) elected not to participate in LDALT after the initial interview with the transplant surgeon.

Reasons for rejecting donors are below:

<table>
<thead>
<tr>
<th>Reason</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient too ill</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Inadequate volume</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Recipient died</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Unsafe donor anatomy</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Abnormal liver function test results</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Medical/psychiatric</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Recipient received cadaveric transplant</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

The most common reason for donor rejection was acute decompensation of the recipient before transplant-
Hilar dissection is performed to isolate the right hepatic artery, portal vein, and bile duct. The arterial branch to segment IV is identified if it originates from the right hepatic artery so that it may be preserved during resection. Operative cholangiography via cystic duct cannulation is performed selectively to evaluate the bile duct anatomy.

Temporary occlusion of the right hepatic artery and portal vein demonstrates the line of demarcation between each lobe (Figure 4). Division of the parenchyma is achieved using a combination of the Harmonic scalpel (Ethicon Endo-Surgery, New Brunswick, NJ), electrocautery, and argon beam coagulation. Division of the parenchyma caudally exposes the hilar plate, which is divided sharply, as is the right hepatic duct. The bridge of the caudate lobe posterior to the portal vein is divided to facilitate passage of the umbilical tape along the anterior aspect of the inferior vena cava exiting between the bifurcation of the hepatic artery and portal vein. The umbilical tape is used as a plumb line to keep the course of the parenchymal transection straight. Complete transection of the parenchyma leaves the right lobe attached only by the main vessels. No inflow vascular occlusion is used during the liver transection. Just before graft procurement, the donor is given 5000 U of intravenous heparin sodium. Vascular clamps are applied, vessels are divided, and the graft is rapidly cooled and flushed with several liters of preservation solution (UW solution, University of Wisconsin–Madison).

Donors are extubated in the operating room and transferred to the Post-Anesthesia Care Unit, where they remain overnight for close monitoring. Because of the rapid regeneration of liver volume, parenteral nutrition is begun on the first postoperative day and continued until oral nutrition is adequate. Deep venous thrombosis prophylaxis is performed with subcutaneous heparin sodium (5000 U twice daily) and pneumocompression boots. Chest physiotherapy and incentive spirometry are also routinely given. Postoperative analgesia is achieved with either epidural infusion of 0.1% bupivacaine or a patient-controlled analgesia pump. All donors are screened daily for postoperative complications.

Helical CT scan with 3-dimensional renderings was excellent in predicting right liver volume (1044±38 g predicted vs 962.7±40 g actual). Helical CT predicted left liver volume as 827±51 g and total liver volume as 1882±73 g. The actual graft weight was 962±40 g and the actual ratio of graft weight to recipient body weight was 1.4±0.1. The percentage of residual donor liver was 48.6%±1.7%. Actual graft volume was 92% of the predicted right lobe liver volume by CT scan. Cooperation between radiologist and surgeon ensures that the proper virtual transection line is used to calculate liver volumes.

Most donors (67%) had significant accessory inferior right hepatic veins (>0.5 cm) that were preserved for reimplantation, with the remainder of donors having a single right hepatic vein. Two donors (13%) were rejected donors were that recipient died during workup (16%) or recipient had transplantation with a cadaveric liver (9%).

Evidence has shown that patients with chronic liver disease who develop acute decompensation have sufficiently poor outcome after LDALT that donor risk cannot be justified. Anatomic exclusion criteria included an estimated graft size less than 0.8% of the recipient's lean body weight, fatty liver (≥20%), or anomalies of the portal or hepatic veins. An anatomic variation of an absent dominant hepatic vein draining the right lobe resulted in 1 donor being rejected (Figure 5). This donor had a right hepatic vein that drains directly into the middle hepatic vein. Although complicated reconstruction is possible with autologous conduit, the decision to expose the donor to significant additional risk in countries where cadaveric transplantation is an option is not considered ethically acceptable by most centers.

Abnormal liver function test results discovered on screening laboratory tests and/or fatty infiltration identified by CT scan and biopsy accounted for approximately 15% of rejected donors. Additional reasons for rejecting donors include a single right hepatic vein (>0.5 cm) that were preserved for reimplantation, with the remainder of donors having a single right hepatic vein. Two donors (13%) were...
identified with simple hepatic cyst and 1 (7%) with hemangioma. These donors were not rejected for these findings. Portal vein anatomy was “normal” in 73% of donors, with the remainder having either portal vein trifurcation (17%) or quadrification (3%; Figure 2D). Three potential donors (6%) had a right posterior portal vein branch originating from the left main portal vein and were excluded. No donor had any major liver abnormality diagnosed on screening CT scan.

Hepatic arterial anatomy was evaluated by 3-dimensional renderings of helical CT scans and angiography. Concordance between helical CT and angiogram was 100%. Most donors (73%) had “normal” hepatic arterial anatomy. Replaced right or left hepatic arteries were seen in 2 (13%) and 1 (7%) donors, respectively. The remaining donor (7%) had both a replaced right and left hepatic artery.

Donors were discharged home an average of 8 days (8.3±0.3 days) after surgery. Operative time was approximately 7 hours (7.02±0.26 hours) for all patients but was approximately 1 to 2 hours shorter when an accessory inferior right hepatic vein was not present. A cell-saver device was used in all donor operations (mean amount of cell saver blood returned to donor, 445±124 mL), with an estimated blood loss that averaged 923±175 mL. Blood transfusion using “banked” blood was not required in any patient. However, autologous units of blood (0.87±0.25 U) received from donors preoperatively were routinely infused to assist in volume resuscitation and to help prevent symptoms related to anemia.

Complications included biloma requiring percutaneous drainage (2 or 11%), temporary radiculoneuropathy (2 or 11%), and symptomatic right pleural effusion (1 or 6%). More serious complications included thrombosis necessitating reoperation (1 or 6%). The portal vein thrombosis was the result of a technical error in

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the closure of the right portal vein branch stump that narrowed the portal vein. This was exacerbated by postoperative liver edema causing an acute angulation at the junction of the main and left portal vein. Simple thrombectomy and closure of the longitudinal venotomy in a transverse fashion corrected the problem. The patient was discharged home in 10 days without anticoagulation and with a patent portal vein. At follow-up of more than 1 year, the patient's portal vein remains patent.

Routine postoperative volumetric CT scans are obtained on both donor and recipients at 7 days and then 1, 3, 6, and 12 months after surgery to assess liver regeneration. No donor regenerated liver volume to his or her original preoperative value with follow-up extending more than 1 year.

**COMMENT**

Living donor liver transplantation is a life-saving surgical innovation that has been shown to be relatively safe and efficacious. Until recently, LDALT has been confined to countries in which cadaveric donation is either limited or prohibited. Because the organ shortage...
has become increasingly more severe throughout Europe and the United States, more centers have embarked on LDALT using right lobe grafts. As reported at the American Society of Transplant Surgeons Meeting in April 2000, 33 centers in the United States have performed 275 LDALTs and 15 centers in Europe have performed nearly 100 LDALTs (Christoph Broelsch, MD, oral communication, September 2000). This number is expected to increase dramatically as additional centers are preparing liver donor programs.

Donor safety must be the primary focus of all discussions concerning LDALT, and primum non nocere (“first do no harm”) must be the dictum followed by the donor selection committee at all times. Although donor safety does not appear to be directly related to the extent of the liver resection performed, most transplant physicians would agree that the selection criteria for right lobe donors should be more stringent with respect to donor age, liver function, and steatosis.17 There are selection criteria that apply to both the donor and recipient that should be addressed separately.18 It is the combination of the favorable and unfavorable characteristics of both the donor and recipient that determine whether the “pair” is suitable for consideration for LDALT.

Before a donor begins evaluation as a live liver donor and again just before the LDALT procedure, a decision is made as to whether the recipient is a medically suitable candidate to undergo the operation. Patients with chronic cirrhotic liver disease and acute decompensation (UNOS status 2A) and those with multiple comorbid medical conditions or extensive previous upper abdominal surgery are not considered as possible LDALT candidates. Trotter et al18 recently reported a 50% rejection rate for LDALT based on recipient characteristics, which was inclusive of patients who were status 2A. Thus, even if a recipient patient identifies a suitable living donor, progression to LDALT cannot be guaranteed.

Our donor evaluation protocol has been refined extensively since its inception and is cost-effective and efficient in donor screening. Prescreening potential donors, by having them forward reports of their blood type and limited laboratory studies confined to liver function tests obtained by the primary care physician, has eliminated the evaluation of obviously incompatible donors. In a recent review by Marcos et al,19 nearly 50% of all donor rejections were due to incompatible blood type. In that donor evaluation model, blood type is obtained as part of step 1, which includes a full history and physical examination of the donor, extensive laboratory and serological studies, and imaging studies that include chest x-ray examination and abdominal ultrasound. Eliminating potential donors with incompatible blood type through primary care physician prescreening eliminates time-consuming and costly evaluation incurred in step 1. In addition, our group has found that 15% of potential donors in our series chose not to pursue LDALT after they have met with a transplant surgeon who describes in detail the evaluation process, recovery period, and complications associated with live liver donation, including death.

All of the advantages of living donor liver transplantation have to be tempered by the risk of injury or death
to a healthy donor. The only benefit to the donor is the psychological benefit of helping to save a loved one. Living donors have expressed extreme satisfaction when allowed to participate in saving a life and take comfort in knowing that they have done everything to help a friend or family member. This has been true even when the outcome of the transplantation has been unsuccessful.

Given the potential risk of harm to the donor, such procedures should be limited to centers with demonstrated excellence in complicated hepatobiliary surgery and established liver transplant programs. Our center had performed more than 1000 liver resection procedures and more than 700 cadaveric transplantations before initiating an LDALT program. Despite this experience, donor morbidity was substantial in this series. The observed complication rate of 67% of donors in this series is significantly higher than that reported in the literature. Critical analysis of surgical outcome would suggest that reported morbidity rates are characteristically underestimated. A stepwise protocol for assessing donor candidacy along with appropriate institutional support, including ethical review boards, dedicated anesthesiology, radiology, internal medicine, psychiatry, nursing, and social work departments, all aid in minimizing donor risk and maximizing safety.

Live donor liver transplantation represents another tool in the armamentarium to treat end-stage liver disease. It will not replace traditional cadaveric transplantation; however, it may offer the possibility of liver transplantation to an additional 15% to 40% of patients waiting on the UNOS list.

Tempered enthusiasm must be maintained in the setting where many centers are considering initiating LDALT programs due to the apparent high success and low donor morbidity rates suggested by others. Since the process of LDALT is still in evolution, it is prudent to establish standard guidelines for donor-recipient pairing, donor evaluation, and surgical technique before applying this technology widely.

Three ethical principles of therapeutic innovation were eloquently outlined by Dr. F. D. Moore in 1988 when the initial debates regarding live donor liver transplantation were first being addressed. The first principle establishes the scientific background on which the procedure is based. Second, the skill, experience, or "field strength" of the team doing the procedure should be evident. Third, the ethical climate of the institution must adequately support the endeavor.

The scientific background and ethical case for LDALT have been established. Results rivaling or exceeding cadaveric transplantation have been observed by a number of centers and only serve to encourage the more widespread application of LDALT. What is less clear is that in the current era of dwindling health care dollars and competitive market forces that challenge the existence of many hospitals, some groups may initiate LDALT programs to maintain "market share" without appropriate "field-strength." As pointed out by Dr. Moore, this is something that the lay public cannot see or feel, and legislative bodies poorly understand, but is clear to physicians.
and surgeons. The establishment of a national database for all LDALT procedures recorded on an intent-to-treat basis will provide physicians and patients with the best understanding of the true outcome of LDALT. Currently, aborted donor operations due to technical misadventures or unanticipated anatomic findings are generally lost to data collection since no transplantation has occurred.

Recently, a modification of the in situ split liver technique has resulted in 2 successful transplantations in adults. Both adult recipients were operated on simultaneously while the donor procurement was under way in an adjacent operating room, resulting in cold ischemic times of less than 2 hours for both recipients. The requirements of 3 experienced teams of anesthesiologists and surgeons, increased duration of donor procurement, and appropriate-sized recipients limit widespread application of this technique; however, it does offer an alternative to live donation and expansion of the adult donor pool.

Given the epidemic in hepatitis C infection and the exponential growth in the UNOS waiting list, a combination of innovative surgical technologies such as split liver transplantation and LDALT are needed to supplement standard cadaveric liver transplantation. Perhaps 1-day xenotransplantation using porcine livers will relegate LDALT to historical significance as an important “bridge” between the era of severe organ shortages, high waiting list mortality, and unlimited resources in treating patients with end-stage liver disease.

Since the presentation of this work at the 81st Annual Meeting of the New England Surgical Society, a total of 100 potential live liver donors have been evaluated, and 31 have provided right lobe liver grafts for LDALT. Three of the 31 LDALT recipients received simultaneous live donor kidney grafts from different donors. The outcome of the 100 donor evaluations is similar to the results reported herein. Donor morbidity has decreased to 38%, with improvements in surgical technique and perioperative medical management.


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REFERENCES


DISCUSSION

Francis D. Moore, Sr, MD, Westwood, Mass: Dr Crombie, Dr Pomfret, it is a privilege to be asked to discuss this absolutely remarkable paper and a chance to review the manuscript. Dr Pomfret and Dr Roger Jenkins and their group first at the Deaconess and now at the Lahey Clinic are to be congratulated on their many contributions to perfection of this seemingly most imposing of all abdominal operations, namely, liver transplantation. And now a scholarly exploration of something that back in the early days of liver transplantation we never even conceived we would have—living adult donors. If this procedure becomes widely feasible and safe and acceptable, it will add tremendously to the available donor pool. It will make real inroads on the huge waiting list with its attendant high mortality. Dr Pomfret has made it clear that there are many complications of this imposing operation, even in her most expert and experienced hands. As with every aspect of organ transplantation, the growth of the field has again demonstrated the surprising association of ethics with statistics: a procedure is ethical depending upon the statistical likelihood both of complications and of success. There have been donor deaths in kidney transplantation, not many, very, very rare, and some of them not reported in the literature. Here is a procedure of greater...
complexity and higher risk. May our profession assure itself
and ourselves and the public that this procedure will always
be undertaken by someone with appropriate laboratory back-
ground, what I call “field strength” in the hospital, a lot of people
associated with liver disease and massive operations and a per-
sonal clinical skill to carry it out safely.

What is Dr Pomfret’s view of the superiority, if any, of family
donors in liver transplantation? I would like her to discuss
her choice and recruitment and acceptance of her living do-
nors. How many related, how many unrelated, and if unre-
lated, why did they volunteer for this remarkable procedure?

This is landmark work that opens up a whole new horizon
in liver transplantation. It is a thrill to have it on our pro-
gram here at the New England Surgical Society where so many
other advances in transplantation were first reported.

Dr Pomfret: It is such an honor and fitting to have Dr
Moore discuss this paper. Prior to starting the live donor pro-
gram at our hospital, I had the opportunity to spend time with
Dr Christoph Broelsch in Germany, who in 1989 performed
the first pediatric live donor liver transplant in the United States
at The University of Chicago. Prior to the first live donor trans-
plantation a great ethical debate and controversy about the pro-
cedure ensued. It was actually Dr Moore’s papers on the ethics
of transplantation and the importance of “field strength” that
provided Professor Broelsch with the ammunition to proceed.
Your papers were discussed again at the XVIII International
Congress of the Transplantation Society held in Rome last month.

There is no apparent immunologic superiority of “re-
lated” donors compared with “unrelated” donors. Interest-
ingly, the worst rejection episode we observed was in a trans-
plantation performed between a son and his mother. For live
donor liver transplantation blood compatibility, internal ve-
nous anatomy and graft size are the most important compo-
nents. Most of our donors were family members but not nec-
essarily genetically related. We performed one live donor trans-
plantation between 2 close friends. We do not accept Good
Samaritan donors at this time.

Doctor: How about a spouse?

Dr Pomfret: We have transplanted the organs of spouses.
In fact, our very first pair was a husband to wife. Because of
the importance of graft size, men donating to women are gen-
erally easier from a volume standpoint than vice versa. In terms
of recruitment, we offer live donor liver transplantation as an
option for appropriate patients. Interested donors are given an
information packet that provides a general overview of the pro-
cess. After that, donors must approach us and volunteer.

ARCHIVES OF INTERNAL MEDICINE

Risk of Venous Thrombosis With Use of Current Low-Dose Oral Contraceptives
Is Not Explained by Diagnostic Suspicion and Referral Bias

Kitty W. M. Bloemenkamp, MD; Fris R. Rosendaal, MD; Harry R. Büller, MD;
Frans M. Helmerhorst, MD; Louise P. Colly, MD; Jan P. Vandenbroucke, MD

Background: The magnitude of the relative risk of venous thrombosis caused by low-dose oral contraceptive use is still de-
bated because previous studies might have been affected by diagnostic suspicion and referral bias.

Methods: We conducted a case-control study in which the effect of diagnostic suspicion and referral bias was excluded. The
study was performed in 2 diagnostic centers to which patients with clinically suspected deep vein thrombosis of the leg were
referred. History of oral contraceptive use was obtained before objective testing for thrombosis. Young females with an ob-
jective diagnosis of deep vein thrombosis were considered case patients, and those who were referred with the same clinical
suspicion but who had no thrombosis served as control subjects. Participants were seen between September 1, 1982, and
October 18, 1995: 185 consecutive patients and 591 controls aged 15 to 49 years with a first episode of venous thrombosis
without malignant neoplasms, pregnancy, or known inherited clotting defects.

Results: The overall odds ratio for oral contraceptive use was 3.2 (95% confidence interval [CI], 2.3-4.5); after adjustment
for age, family history of venous thrombosis, calendar time, and center, the odds ratio was 3.9 (95% CI, 2.6-5.7). In the idiopathic group (120 patients and 413 controls, excluding recent surgery, trauma, or immobilization), the odds ratio for oral contraceptive use was 3.8 (95% CI, 2.5-5.9); after adjustment, the odds ratio was 5.0 (95% CI, 3.1-8.2).

Conclusions: In this study, in which patients and controls were subject to the same referral and diagnostic procedures, we
found similar relative risk estimates for oral contraceptive use as in previous studies. We conclude that diagnostic suspicion
and referral bias did not play an important role in previous studies and that the risk of venous thrombosis with use of current
brands of oral contraceptives still exists. (1999;159:65-70)

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