

Care pathways for ectopic pregnancy: a population-based cost-effectiveness analysis

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Objective: To define care pathways in terms of frequency, costs, and outcomes and to assess their cost-effectiveness.

Design: Population-based cost-effectiveness study.

Setting: Auvergne EP registry (France).

Patient(s): Women (n = 1,664) registered between 1994 and 2003.

Intervention(s): Standard diagnosis and treatment of EP.

Main Outcome Measure(s): Costs before, during, and after hospitalization were assessed from data concerning medical costs of examinations and treatments. One-year fertility was used for effectiveness assessment. We assessed cost-effectiveness for the healthcare system.

Result(s): Diagnostic ultrasound (47% of scans were nondiagnostic) was essential for the use of methotrexate as a first-line treatment for subacute EP. Hospital and ambulatory care costs were similar for all surgical-care pathways (diagnostic or nondiagnostic ultrasound scan followed by conservative or radical laparoscopy). Hospital and ambulatory-care costs associated with methotrexate treatment were less than half those for surgical-care pathways. In subacute cases, conservative treatments, and methotrexate in particular, were associated with better fertility at similar or lower cost to salpingectomy for EP for reproductive failure.

Conclusion(s): Conservative treatments are cost-effective with respect to salpingectomy, when subsequent fertility is at stake. Efforts should be made to increase the frequency of diagnostic ultrasound scans, making it possible to increase methotrexate use and cost-effectiveness. (*Fertil Steril*® 2007;87:737–48. ©2007 by American Society for Reproductive Medicine.)

Key Words: Pregnancy, ectopic, cost, care, cost-effectiveness

After a period of decline in industrialized countries, the incidence of ectopic pregnancy (EP) has now stabilized at around 1.5% of pregnancies, or has slightly increased, due to augmented rate of EP resulting from reproductive failure (1–3). This slight increase (accounted for by recent increases in chlamydial infections or in smoking in women of reproductive age) is worrying because this type of EP has serious consequences for the subsequent fertility of the woman (infertility in 40% and recurrence in 30% of cases at 2 years) (4).

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Ectopic-pregnancy care also poses complex questions. Improvements in diagnostic methods over the last 3 decades have facilitated earlier diagnosis (before rupture), leading to the development of new surgical and nonsurgical procedures for the conservative management of EP and the Fallopian tube (5). However, despite a large number of noncontrolled studies and a much smaller number of controlled studies comparing the outcomes (immediate success, middle-term fertility) of various alternatives (6), it remains unclear whether treatment should be conservative (salpingostomy) or radical (salpingectomy), whether conservative management should be drug based, and whether surgical intervention should be laparotomic or laparoscopic (7). Economic issues are also of increasing relevance in the context of limited resources and rising concern within society that increases in expenditure should be justified by significant health benefits. However, few studies have compared the costs and cost-effectiveness of different care procedures for EP (8–14).

This study, based on the data from the population-based registry of EPs in the Auvergne region (in the center of France), aimed to define and assess care pathways in terms of frequency, costs, and outcomes and to evaluate their cost-effectiveness in situations in which the patient's clinical characteristics were compatible with several different treatment options for EP. Data from the registry concerning medical costs of examinations and treatments before, during, and after hospitalization were used to evaluate the whole sequence of care costs, from the first suspicion of EP to subsequent follow-up and possible future pregnancy, from the point of view of the healthcare system. We considered 1-year fertility to be the most relevant outcome for assessing care pathways, and we distinguished *acute EP* (requiring emergency care as a result of tubal rupture and abundant hemoperitoneum) from *classical subacute EP* because the management procedures (and pathways) clearly differ between these two types of EP (conservative drug treatment is inappropriate for EP with abundant hemorrhaging, for example).

MATERIALS AND METHODS

Study Population and Data Collected in the Registry

This study was based on data from the Auvergne EP registry collected from July 1994 to December 2003. The characteristics of this EP register have been described elsewhere (15, 16). Briefly, all women aged 15–44 years, resident in three départements (administrative units: Cantal, Allier, and Puy de Dôme) in the Auvergne Region in the center of France, and who were treated for EP in one of the area centers were registered and prospectively followed until the age of 45 years, and their reproductive outcomes were studied. At each center, a trained investigator (a midwife or a physician) is responsible for case identification, follow-up, and data collection.

The information collected for each woman includes the following: sociodemographic characteristics and place of residence; gynecological, reproductive, and surgical histories; conditions of conception; smoking habits; characteristics of the EP (site, rupture, hemoperitoneum); and all diagnostic and therapeutic procedures (and their order) during hospitalization. For follow-up, the women are interviewed every 6 months by telephone about whether they wish to become pregnant again, whether they manage to become pregnant again, time to pregnancy (or time at risk of pregnancy), use of contraception or medical measures related to infertility, and obstetric outcome (if pregnancy occurred). From April 1999 onward, additional data concerning healthcare visits (general practitioners, specialists, and nurses), diagnostic procedures (laboratory and imaging), and treatments before and after hospitalization also were prospectively collected.

During hospitalization, data were collected for all radiological examinations (including vaginal ultrasound scans); laboratory tests (including β -hCG, liver tests, and complete

blood-cell count); drug consumption (including antibiotics and anticoagulants); blood transfusions; therapeutic procedures, whether drug-based (methotrexate) or surgical (for example, *conservative*, i.e., salpingostomy, or *radical*, i.e., salpingectomy); and duration of hospital stay. Before and after hospitalization, data were collected concerning consultations with general practitioners and gynecologists, nursing care, drugs, laboratory tests and ultrasound scans, and sick leave. The data concerning medical care after hospitalization were collected by means of a questionnaire that was mailed to the women 2 months after discharge.

Definition of Care Pathways

We defined the *hospital care pathways* that are followed by patients, on the basis of the diagnostic- and therapeutic-procedure data from the registry. Pathways were represented as a tree, with each patient entering at the same point: ultrasound examination. Hospital care pathways were analyzed according to the need for emergency care as a result of tubal rupture and abundant hemoperitoneum: a woman was considered to have acute EP if she required resuscitation before treatment or had an intra-abdominal hemorrhage plus a maximum of 1 day between the first β -hCG determination and treatment.

Assessment of Costs Associated With Care Pathways

The costs associated with EP care were assessed from the point of view of the healthcare system. For the assessment of direct costs—those directly attributable to EP care—adopting the healthcare system perspective led us to concentrate on hospital and ambulatory costs. The assessment of indirect costs, relating primarily to losses of productivity in patients in active employment, was based on the daily allowances provided by the healthcare system (the national health insurance system) for working days lost as a result of EP.

On the basis of the data provided by the registry for the diagnostic and therapeutic procedures performed for EP care, hospital care costs were calculated by using the national hospital-cost database, giving estimates that were representative at the national level. The national hospital-cost database for 2005, based on a sample of 50 public and private nonprofit hospitals (3.4 million hospital stays; database available at <http://www.atih.sante.fr>), uses accounting data to estimate the cost per diagnosis-related group (DRG; 771 DRG in total). Because the ectopic-pregnancies DRG is specific to this condition, grouping together all the different kinds of EP, estimations of hospital costs were free of the biases that may occur when the DRG is a composite index of diseases.

The costs of diagnostic and therapeutic procedures involved in hospital care for EP were calculated by determining DRG unit values of indices (B for laboratory procedures, and RCI for relative cost indices relating to surgical and imaging procedures), with the number of B or RCI involved

in each procedure taken from the Medical Procedure Catalogue (for more information, see the French guidelines for the economic evaluation of healthcare technologies at <http://www.ces-asso.org> [English version available]). Information concerning the drugs administered during hospitalization was available from the registry (data were available for the principal drugs administered: antibiotics, anticoagulants, and methotrexate) and from the national hospital-cost database (mean cost of drugs per hospitalization in the ectopic-pregnancies DRG represented 0.96% of the total mean cost per stay).

Data on methotrexate, in particular, were required to assess the cost-effectiveness of this treatment option. However, partial information on drugs from the registry led to the overestimation of this component of the cost of hospitalization because of the addition of the costs of drugs reported in the registry to the mean cost of drugs per day of hospitalization derived from the national hospital-cost database. This slight overestimation of the costs of drugs (a 3% difference in cost with respect to underestimation because of the exclusion of drug costs derived from the national hospital-cost database) had no impact on the outcome of the cost-effectiveness analysis, because it concerned all the care options considered to a similar extent.

The national hospital-cost database was also used to assess costs not directly attributable to the diagnostic and therapeutic procedures reported in the registry but that nevertheless contributed to the cost of hospital care, such as salaries (nurses, etc.), medical consumables, depreciation of equipment, and logistics costs (laundry, catering, administrative staff, etc.). These service-center costs can be obtained from the national hospital-cost database. They were expressed as mean service-center cost per day of hospitalization in the ectopic-pregnancies DRG, and their contribution to the costs associated with hospital care pathways was then assessed on the basis of the duration of hospitalization reported in the registry.

Medical costs incurred before and after hospitalization were also assessed from the point of view of the healthcare system. This assessment was based on the fees-for-service and tariffs of the Common Classification of Medical Procedures (<http://www.atih.sante.fr>). Costs related to sick leave caused by EP (hospital stay and sick leave before and after hospitalization) were evaluated on the basis of the 41.26-euros daily allowance provided by the French national health insurance system.

Total direct medical costs (hospital and ambulatory care) were calculated taking into account all medical costs relating to EP care both within and outside the hospital. The total costs of hospitalization were calculated as the sum of costs at each step of the care pathway (diagnosis, first-line treatment, and possibly, second-line treatment). For care pathways including first-line treatment failure, the costs associated with second-line treatments were included in the calculation of the total cost of the care pathway, taking into account the

frequency of first-line treatment failure. All costs were expressed in euros, based on 2005 tariffs.

Assessment of Subsequent Fertility According to Care Pathway Followed

Subsequent fertility after EP treatment was considered to be the relevant outcome associated with care pathways. Fertility was measured as the frequency of women becoming pregnant (intrauterine pregnancy) during a 1-year period in which they were trying to conceive. Because the length of time between EP and first attempt to get pregnant was likely to vary between women, fertility was assessed in the women who began trying to get pregnant during the 2 years after EP. Women aged younger than 18 or older than 45 years, women who had been sterilized, and those who declared that they did not wish to have any more children were excluded from the analysis.

Assessment of the Cost-Effectiveness of Care Pathways

The cost-effectiveness analysis was designed to compare EP care pathways in terms of costs to the healthcare system and subsequent fertility: we assumed that 1,000 hypothetical women entered each of the care pathways studied (methotrexate or laparoscopy performed conservatively or radically). We assumed that all the women tried to get pregnant during the 2 years after treatment for EP. The cost-effectiveness analysis therefore involved comparing total costs (reflecting the resources allocated to EP care, given that these resources could have been allocated for other purposes), with the total expected outcome of this allocation (intrauterine pregnancies). A given first-line treatment was preferred to another if it was more effective at lower cost.

Statistical analysis was based on exact χ^2 tests and Wilcoxon tests on the ranks of individual costs, with 95% confidence intervals when appropriate (i.e., when the data followed a normal or binomial distribution).

RESULTS

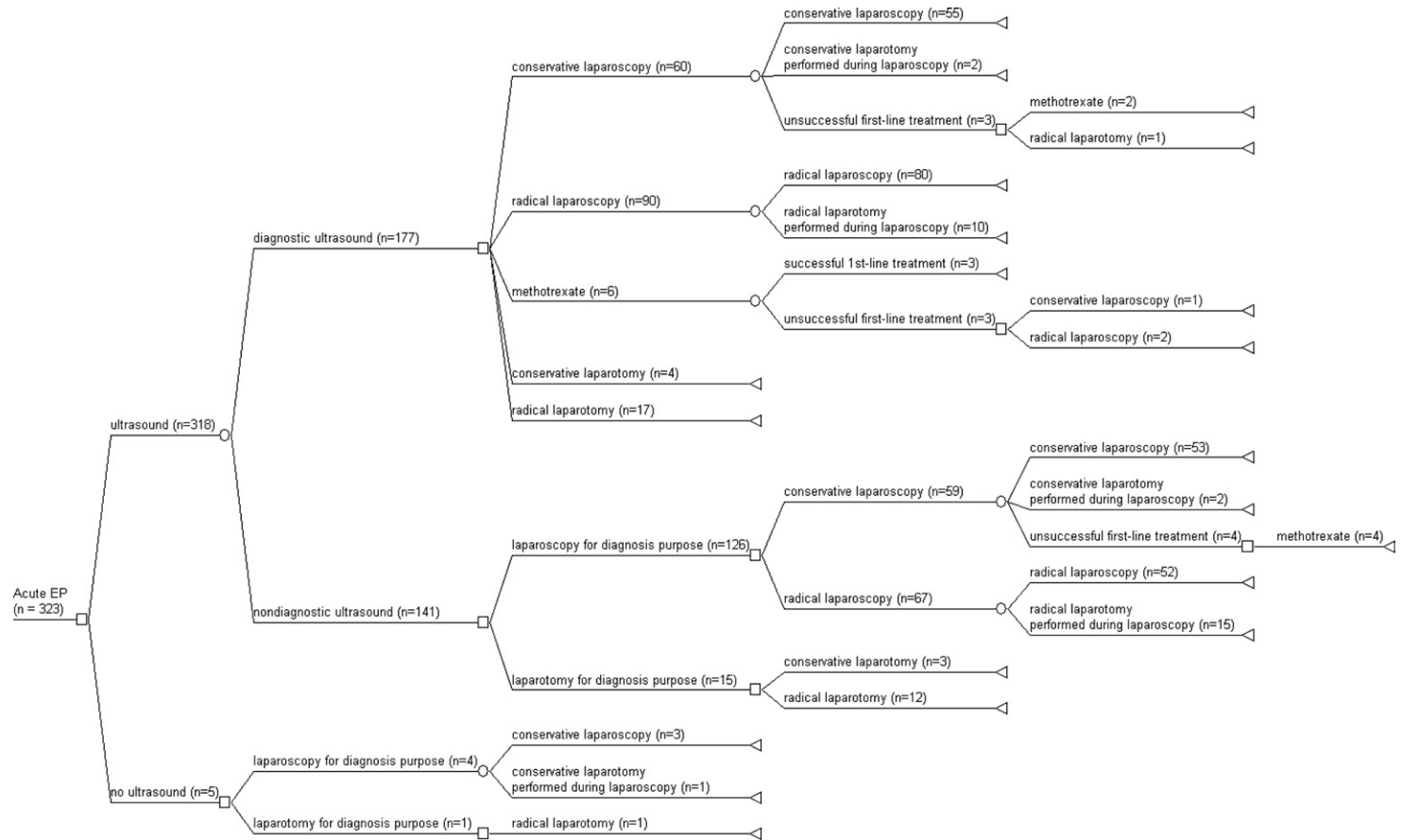
Care Pathways

Between July 1, 1994 and December 31, 2003, 1,808 women were included in the EP registry. Diagnosis or treatment data were missing for 145 women, so only 1,664 women were included in the care-pathways analysis. Overall, 500 EP cases resulted from contraceptive failure and 1,164 cases resulted from reproductive failure. Acute EP (as defined in the paragraph immediately preceding the start of the Materials and Methods section) accounted for 323 cases, with the remaining 1,341 EP cases being considered subacute. Acute cases resulted more frequently from contraceptive failure than from reproductive failure (24% vs. 17%, $P=.002$).

Hospital care pathways were defined for all cases of acute and subacute EP (Figs. 1 and 2). All care pathways began with ultrasound examination (whether the results were diagnostic or not) and were characterized by the first-line treat-

FIGURE 1

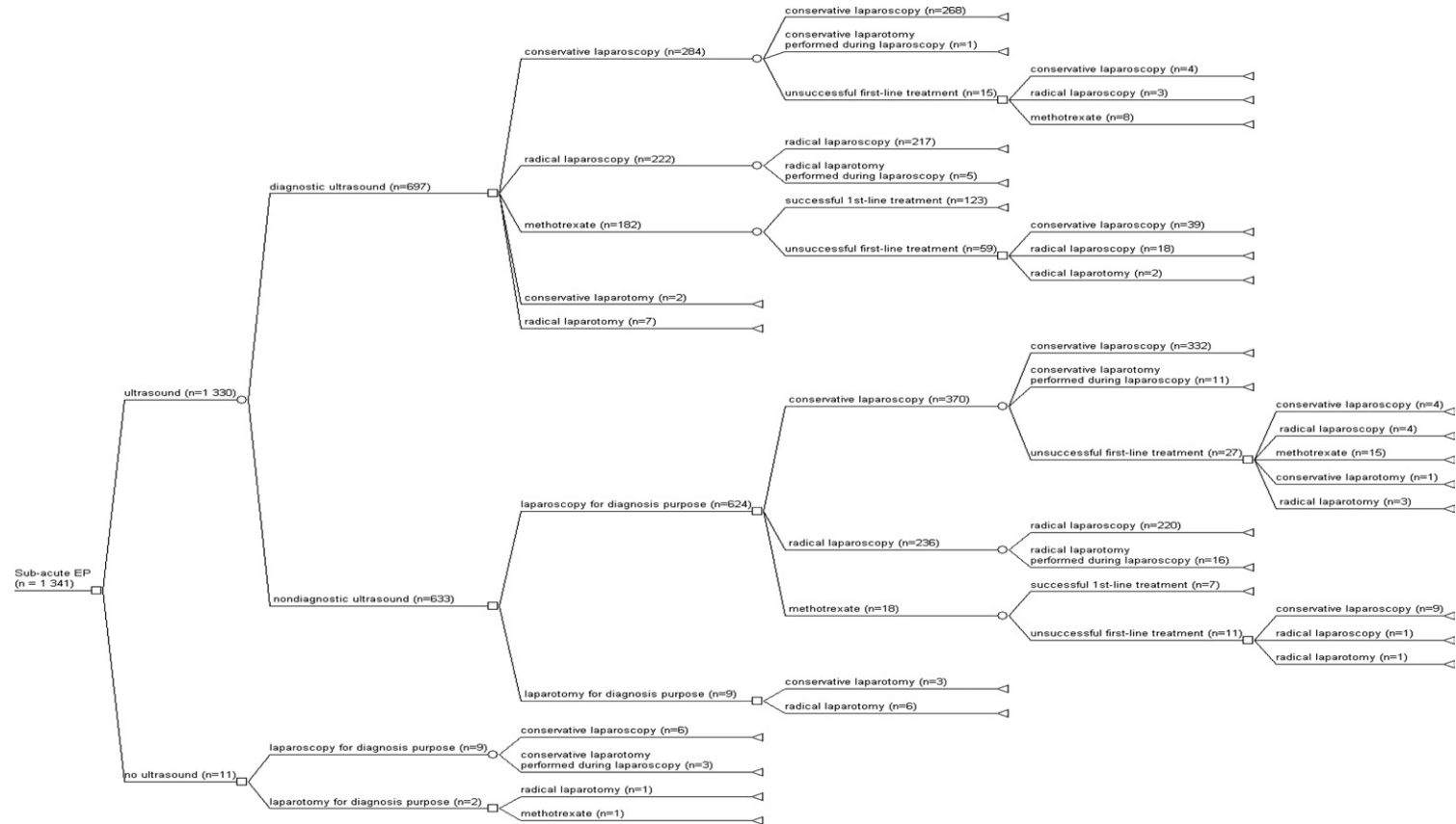
Hospital care pathways for acute EP (n = 323). The tree depicts the course of diagnosis and treatment for the patients. The decision nodes, generally represented as squares, represent medical choices between surgical and medical procedures whereas the chance nodes, shown as circles, represent a point in time at which more than one possible event may occur. For example, conservative laparoscopy may have resulted in successful care for EP but, when unsuccessful, further drug-based or surgical treatment had to be initiated. The probability of patients progressing down a given pathway at a chance node was determined from an outcome frequency obtained from the registry data.



Seror. Cost-effectiveness of ectopic pregnancy care pathways. *Fertil Steril* 2007.

FIGURE 2

Hospital care pathways for subacute EP (n = 1,341). The tree depicts the course of diagnosis and treatment for the patients. The decision nodes, generally represented as *squares*, represent medical choices between surgical and medical procedures, whereas the chance nodes, shown as *circles*, represent a point in time at which more than one possible event may occur.



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TABLE 1

Hospitalization costs in Euros, according to care pathways for subacute and acute ectopic pregnancy (N = 751).

| Care pathway | Ultrasound | β -hCG determination | Other laboratory investigations ^a | Curettage | 1st-line treatment | 2nd-line treatment ^b | Drugs (apart from MTX) | Other medical costs ^c | Logistic costs ^c | Hospital cost per patient |
|--|------------|----------------------------|--|-----------|--------------------|---------------------------------|------------------------|----------------------------------|-----------------------------|---------------------------|
| Subacute ectopic pregnancies (n = 604) | | | | | | | | | | |
| CL-DU | | | | | | | | | | |
| Median | 45.5 | 9.7 | 97.1 | 0 | 608 | 0 | 4.1 | 385.6 | 216.9 | 1,615.2 |
| Range | 0-227.5 | 0-58.4 | 33.1-357.3 | 0-288 | 608-608 | 0-608 | 0-4.1 | 0-1,349.5 | 0-759 | 686.2-2,983 |
| CL-nDU | | | | | | | | | | |
| Median | 45.5 | 9.7 | 129.3 | 0 | 608 | 0 | 0 | 371.4 | 208.9 | 1,528.3 |
| Range | 0-273 | 0-48.7 | 29.2-371 | 0-144 | 592-608 | 0-608 | 0-4.1 | 0-1,857.1 | 0-1,044.5 | 682.8-3,678.1 |
| RL-DU | | | | | | | | | | |
| Median | 45.5 | 9.7 | 101 | 0 | 464 | — | 4.1 | 627.3 | 352.8 | 1,616.7 |
| Range | 0-182 | 0-39 | 22.4-294.3 | 0-288 | 464-592 | — | 0-4.1 | 0-1,463.7 | 0-823.2 | 576.7-3,150.1 |
| RL-nDU | | | | | | | | | | |
| Median | 45.5 | 9.7 | 119.5 | 0 | 464 | — | 4.1 | 627.3 | 352.8 | 1,632.7 |
| Range | 0-182 | 0-39 | 33.1-295.3 | 0-288 | 464-592 | — | 0-4.1 | 0-2,091 | 0-1,176 | 516.9-4,186.4 |
| MTX-nDU | | | | | | | | | | |
| Median | 91 | 9.7 | 104.9 | 0 | 4.9 | 0 | 0 | 126.5 | 71.2 | 525.2 |
| Range | 0-364 | 0-87.7 | 0-508.5 | 0-288 | 4.9-4.9 | 0-1,056.1 | 0-4.1 | 0-875.1 | 0-492.1 | 27.3-2,197.0 |
| Acute ectopic pregnancies (n = 147) | | | | | | | | | | |
| CL-DU | | | | | | | | | | |
| Median | 45.5 | 9.74 | 80.85 | 72 | 608 | 0 | 0 | 405.1 | 227.9 | 1,535.7 |
| Range | 0-136.5 | 0-19.5 | 11.7-165 | 0-288 | 592-608 | 0-4.9 | 0-4.1 | 32.7-1,012.8 | 18.4-569.6 | 992.7-2,513.7 |
| CL-nDU | | | | | | | | | | |
| Median | 45.5 | 9.7 | 119.5 | 0 | 608 | 0 | 4.1 | 589.3 | 331.4 | 1,717.4 |
| Range | 0-136.5 | 0-29.2 | 41.9-239.8 | 0-144 | 608-608 | 0-4.9 | 0-4.1 | 0-1,178.6 | 0-662.8 | 727.8-2,648.1 |
| RL-DU | | | | | | | | | | |
| Median | 45.5 | 9.7 | 96.3 | 0 | 464 | 0 | 4.13 | 627.3 | 352.8 | 1,599.8 |
| Range | 0-182 | 0-29.2 | 33.1-296.5 | 0-144 | 464-592 | 0-464 | 0-4.1 | 0-1,463.7 | 0-823.2 | 632.2-3,178.5 |
| RL-nDU | | | | | | | | | | |
| Median | 45.5 | 9.7 | 126.8 | 0 | 464 | — | 4.1 | 627.3 | 352.8 | 1,678.8 |
| Range | 0-91 | 0-19.5 | 34.1-231.5 | 0-144 | 464-592 | — | 0-4.1 | 0-1,672.8 | 0-940.8 | 642.9-3,381.6 |

Note: CL = conservative laparoscopy; CR = radical laparoscopy; MTX = methotrexate; DU = diagnostic ultrasound; nDU = nondiagnostic ultrasound.

^a Other laboratory investigations included blood-cell count, ionogram, C-reactive protein, blood-group determination, and so on.

^b Average costs of second-line treatments according to the frequencies of first-line treatment failures.

^c According to the national hospital-cost database from the French DRG program.

TABLE 2

Outpatient costs per patient in Euros, according to care pathways for subacute and acute ectopic pregnancy.

| Care pathway | Outpatient care before hospitalization | | | | Outpatient care after hospitalization | | | | | | Sick leave ^b | |
|---|--|------------|----------------------------|------------------|---------------------------------------|------------|----------------------------|--|--------------|------------------|-------------------------|------------------|
| | Consultations | Ultrasound | β -hCG determination | Cost per patient | Consultations | Ultrasound | β -hCG determination | Other laboratory investigations ^a | Nursing care | Cost per patient | No. of days | Cost per patient |
| Subacute ectopic pregnancies: (n = 604 before hospitalization; n = 315 after hospitalization) | | | | | | | | | | | | |
| CL-DU | | | | | | | | | | | | |
| Median | 23 | 0 | 13.5 | 56.5 | 21.2 | 0 | 12.4 | 0 | 0 | 84.5 | 10 | 412.6 |
| Range | 0-129 | 0-283.5 | 0-121.5 | 0-463 | 0-267.4 | 0-209.1 | 0-99.6 | 0-27.4 | 0-135.4 | 0-335.9 | 0-79 | 0-3,259.5 |
| CL-nDU | | | | | | | | | | | | |
| Median | 23 | 0 | 13.5 | 59.8 | 20.4 | 0 | 12 | 0 | 0 | 56.4 | 3.5 | 144.4 |
| Range | 0-241 | 0-226.8 | 0-94.5 | 0-402.6 | 0-135 | 0-201.4 | 0-95.9 | 0-36 | 0-123.5 | 0-556.5 | 0-76.5 | 0-3,156.4 |
| RL-DU | | | | | | | | | | | | |
| Median | 23 | 0 | 13.5 | 59.5 | 23 | 0 | 13.5 | 0 | 0 | 50 | 5 | 206.3 |
| Range | 0-169 | 0-283.5 | 0-67.5 | 0-379 | 0-161 | 0-170.1 | 0-54 | 0-27 | 0-146.8 | 0-344.4 | 0-72 | 0-2,970.7 |
| RL-nDU | | | | | | | | | | | | |
| Median | 23 | 0 | 0 | 46 | 23 | 0 | 13.5 | 0 | 0 | 83.3 | 18 | 742.7 |
| Range | 0-138 | 0-170 | 0-54 | 0-282.4 | 0-86 | 0-113.4 | 0-54 | 0-31 | 0-146.9 | 0-242.8 | 0-163 | 0-6,725.4 |
| MTX-nDU | | | | | | | | | | | | |
| Median | 46 | 0 | 13.5 | 77 | 16 | 17.2 | 12.3 | 0 | 0 | 65.5 | 4 | 165 |
| Range | 0-184 | 0-453.6 | 0-108 | 0-637.6 | 0-112.3 | 0-158.2 | 0-75.3 | 0-13.2 | 0-66 | 0-330.7 | 0-27.5 | 0-1,134.7 |
| Acute ectopic pregnancy: (n = 147 before hospitalization; n = 91 after hospitalization) | | | | | | | | | | | | |
| CL-DU | | | | | | | | | | | | |
| Median | 23 | 0 | 0 | 23 | 22.3 | 0 | 13.1 | 0 | 0 | 92.8 | 14.5 | 599.6 |
| Range | 0-69 | 0-56.7 | 0-40.5 | 0-152.7 | 2.8-102.7 | 0-109.9 | 0-104.6 | 0-18.3 | 0-134.7 | 8.2-292.8 | 1-54 | 41.26-2,228 |
| CL-nDU | | | | | | | | | | | | |
| Median | 23 | 0 | 0 | 43 | 21.6 | 0 | 12.7 | 0 | 0 | 79.7 | 4.5 | 185.7 |
| Range | 0-86 | 0-56.7 | 0-40.5 | 0-110.2 | 0-64.8 | 0-106.5 | 0-76.1 | 0-25.4 | 0-96.2 | 0-298 | 2-24.5 | 82.52-1,010.9 |
| RL-DU | | | | | | | | | | | | |
| Median | 23 | 0 | 0 | 23 | 23 | 0 | 13.5 | 0 | 0 | 79.7 | 8 | 330.1 |
| Range | 0-103 | 0-56.7 | 0-13.5 | 0-156.7 | 0-106 | 0-113.4 | 0-94.5 | 0-31.1 | 0-140.5 | 0-285.4 | 0-97 | 0-4,002.2 |
| RL-nDU | | | | | | | | | | | | |
| Median | 23 | 0 | 0 | 23 | 43 | 0 | 0 | 0 | 0 | 79.7 | 12 | 495.1 |
| Range | 0-132 | 0-283.5 | 0-40.5 | 0-413 | 0-132 | 0-113.4 | 0-54 | 0-27 | 0-140.5 | 0-414.9 | 2-53 | 82.5-2,186.8 |

Note: CL = conservative laparoscopy; CR = radical laparoscopy; MTX = methotrexate; DU = diagnostic ultrasound; nDU = nondiagnostic ultrasound.

^a Other laboratory investigations included blood cell count, ionogram, C-reactive protein, *Chlamydia trachomatis* serological tests, and so on.

^b Sick leave before, during, and after hospitalization.

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TABLE 3**Total costs of care per ectopic pregnancy according to hospital-care pathway.**

| Care pathway ^a | Hospital costs (€) | Hospital and outpatient care costs (€) | Total costs, including sick leave (€) |
|--|--------------------------|--|---------------------------------------|
| Subacute ectopic pregnancies (n = 315) | | | |
| CL-DU | | | |
| Median | 1,616.2 | 1,784.1 | 2,195.9 |
| Range | 686.2–2,983 | 800.6–3,393.3 | 884.3–6,664.9 |
| Mean | 1,639.1 | 1,821.9 | 2,376.9 |
| CL-nDU | | | |
| Median | 1,510.1 | 1,671 | 2,061.2 |
| Range | 698.6–3,678.1 | 833.4–3,966.5 | 833.4–5,278.2 |
| Mean | 1,609.1 | 1,791.7 | 2,196.5 |
| CL (DU and nDU) | | | |
| Median | 1,603.7 | 1,740.2 | 2,144.7 |
| Range | 686.2–3,678.1 | 800.6–3,966.5 | 833.4–6,664.9 |
| Mean | 1,623.5 | 1,806.3 | 2,283.3 |
| RL-DU | | | |
| Median | 1,626.7 | 1,806.2 | 2,104.7 |
| Range | 576.7–3,063.7 | 691.2–3,226.9 | 816.6–4,925.2 |
| Mean | 1,546.6 | 1,722.7 | 2,284.2 |
| RL-nDU | | | |
| Median | 1,685.3 | 1,854.7 | 2,516.3 |
| Range | 616.6–4,186.4 | 716.6–4,327.4 | 716.6–9,208.7 |
| Mean | 1,687.3 | 1,859 | 2,691.1 |
| RL (DU and nDU) | | | |
| Median | | | |
| Range | 1,656.6 | 1,819.7 | 2,200.6 |
| Mean | 576.7–4,186.4 1,610.1 | 691.2–4,327.4 1,784.3 | 716.6–9,208.7 2,468 |
| MTX-DU | | | |
| Median | 454.5 | 670.5 | 1,006.3 |
| Range | 27.3–2,197 | 69.5–2,399.9 | 69.5–2,826 |
| Mean | 643.1 | 834.7 | 1,083.8 |
| Acute ectopic pregnancies (n = 91) | | | |
| CL-DU | | | |
| Median | 1,648.2 | 1,765.8 | 2,568.4 |
| Range | 992.7–2,513.7 | 1,043.9–2,686.5 | 1,082.6–4,832.7 |
| Mean | 1,755.2 | 1,904.7 | 2,600.4 |
| CL-nDU | | | |
| Median | 1,717.4 | 1,829.3 | 2,265.7 |
| Range | 727.8–2,648.1 | 750.8–2,848.6 | 1,370.9–3,701.3 |
| Mean | 1,745 | 1,892.6 | 2,310.1 |
| CL (DU and nDU) | | | |
| Median | 1,717.4 | 1,829.3 | 2,400.7 |
| Range | 727.8–2,648.1 | 750.8–2,848.6 | 1,082.6–4,832.7 |
| Mean | 1,749.7 | 1,898.2 | 2,444.1 |
| RL-DU | | | |
| Median | 1,572.7 | 1,680 | 2,565.6 |
| Range | 632.2–3,178.5 | 718.2–3,317.5 | 718.2–5,077.3 |
| Mean | 1,659.9 | 1,787.6 | 2,532.8 |

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TABLE 3

Continued.

| Care pathway ^a | Hospital costs (€) | Hospital and outpatient care costs (€) | Total costs, including sick leave (€) |
|---------------------------|--------------------|--|---------------------------------------|
| RL-nDU | | | |
| Median | 1,724.5 | 1,918.4 | 2,552.4 |
| Range | 1,234–3,381.6 | 1,428–3,673.9 | 1,623.4–5,579.8 |
| Mean | 1,923.2 | 2,105.3 | 2,752.5 |
| RL (DU and nDU) | | | |
| Median | 1,626.9 | 1,782.6 | 2,559 |
| Range | 632.2–3,381.6 | 718.2–3,673.9 | 718.2–5,579.8 |
| Mean | 1,756.1 | 1,903.7 | 2,613.1 |

Note: CL = conservative laparoscopy; CR = radical laparoscopy; MTX = methotrexate; DU = diagnostic ultrasound; nDU = nondiagnostic ultrasound.

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ment provided. For subacute EP, five main pathways were identified, corresponding to 97% of cases: first-line treatment was most often methotrexate or conservative or radical laparoscopy in cases in which ultrasound examination was diagnostic or was conservative or radical laparoscopy in cases in which ultrasound examination was not diagnostic.

For acute EP, four pathways accounted for 85% of cases: the first-line treatment was laparoscopy, which was conservative or radical with the care pathways depending on whether the ultrasound scan was diagnostic. The frequency of nondiagnostic ultrasound scans did not differ according to the acute or subacute status of the EP (46% vs. 47%), and the choice of surgical first-line treatment (conservative or radical laparoscopy) did not depend on whether ultrasound examinations were diagnostic or not. However, laparoscopy was more frequently conservative for subacute EP, regardless of ultrasound results ($P < .003$).

The use of methotrexate as a first-line treatment for subacute EP depended on the initial ultrasound scan being diagnostic. Consistent with this, our data showed that the frequencies of both diagnostic ultrasound examinations and the use of methotrexate as a first-line treatment increased with time ($P < .0001$ for trend).

No difference in first-line treatment according to the origin of the EP (contraceptive or reproductive failure) was observed for acute EP, regardless of ultrasound results. In contrast, first-line treatment for subacute EP depended on the cause of the EP: after the diagnosis of subacute EP by ultrasound scan, first-line treatment was more frequently methotrexate or conservative laparoscopy for EP caused by reproductive failure (71% vs. 59%, $P = .009$).

Costs Associated With EP Care Pathways

Costs incurred before and during hospitalization were assessed by using data from 751 women who were included

after April 1, 1999. Costs after hospitalization were finally calculated for only 406 women, as a result of questionnaires not being returned and missing data. The subsamples of 751 and 406 EP cases used to assess costs were representative of the whole sample of 1,664 EP cases in terms of EP severity (proportions of acute and subacute EP cases); the origin of EP (proportions of reproductive and contraceptive failure); frequency of nondiagnostic ultrasound scans; first-line treatment failure rates; and the frequencies of all care pathways except for methotrexate for subacute EP care, which was slightly overrepresented in the subsamples used to assess care costs (19% vs. 14%, $P = .005$). Note that the recent increase in the use of methotrexate had no impact on the results of the cost-effectiveness analysis, as each care pathway was assessed independently.

Costs were calculated separately for acute and subacute EP care and are presented in Table 1 (hospital care), Table 2 (ambulatory care), and Table 3 (total costs). Hospital costs associated with surgical-care pathways (diagnostic or nondiagnostic ultrasound followed by conservative or radical laparoscopy) were largely similar ($P = .70$), ranging from 1,500 to 1,700 euros per patient. In contrast, the hospital costs associated with the drug-based care pathway (methotrexate) were less than half those of the surgical-care pathways ($P < .0001$). However, for subacute EP care, costs before hospitalization were highest for women subsequently treated with methotrexate (median cost, 77 vs. 58 euros; P value for the exact Wilcoxon test = 0.0008), because these women consulted their doctors more often ($P = .0004$) and underwent more β -hCG determinations ($P = .0001$).

Pre-hospitalization costs did not differ according to the type of surgical treatment subsequently provided to women with acute EP (or subacute EP), but ambulatory costs before hospitalization were lower for women with acute EP than for those with subacute EP (median cost, 23 vs. 57 euros; $P < .0001$): women with acute EP consulted their doctors less

frequently ($P=.0006$) and underwent less frequent ultrasound examinations ($P<.0001$) and β -hCG measurements ($P<.0001$). No difference was found in post-hospitalization costs according to the type of surgical treatment or type of EP (acute or subacute). However, medical costs after hospitalization were higher if the hospital care pathway for subacute EP was drug-based rather than surgical (median cost, 130 vs. 80 euros; $P=.0009$), because patients had more ultrasound examinations and β -hCG determinations ($P<.0001$).

Overall, the ambulatory and hospital costs of care for acute or subacute EP ranged from 1,700 euros to 1,900 euros when the first-line treatment was surgical, whereas these costs amounted to about 700 euros for subacute EP treated with methotrexate. The amount of sick leave taken before and after hospitalization did not differ according to hospital care pathway or type of EP. In particular, no difference in the amount of sick leave taken was observed between drug-based and surgical-care pathways for subacute EP.

The cost of treating acute and subacute EP did not depend on the origin of the EP (contraceptive or reproductive failure), with no difference in medical costs found before, during, or after hospitalization, regardless of the hospital care pathway considered. The origin of the EP also had no effect on the length of hospital stay or sick leave before and after hospitalization.

Fertility After EP Care and Efficacy of Care Pathways

Fertility assessment was based on the data for 630 women with EP caused by reproductive failure and at least 3 years of follow-up (to ensure a period of at least 1 year of trying to get pregnant for women who began trying for a new pregnancy in the 2 years after the index EP). This subsample did not differ from the whole sample of reproductive-failure EP ($n = 1,164$) in terms of the type of EP (acute or subacute) and the care pathways. We were unable to assess fertility rates after acute EP care because of the small number of intrauterine pregnancies per hospital care pathway.

For subacute EP cases, 20% of women did not try to get pregnant again after EP care, and 8% opted for IVF treatment. Of the remaining women, 26% did not succeed in getting pregnant, and 52% had intrauterine pregnancies leading to the birth of a child (Table 4). Similar fertility rates were obtained with conservative treatments: methotrexate (57%; 95% confidence interval, 42%–71%) and conservative laparoscopy (54%; 95% confidence interval, 48%–61%); radical laparoscopy (salpingectomy) gave the lowest fertility rate (44%; 95% confidence interval, 34%–54%, $P<.0001$). These rates were not affected by the diagnostic or nondiagnostic nature of the ultrasound examination before treatment.

Cost-Effectiveness of Subacute Ectopic Pregnancy Care Pathways

On the basis of the results presented above, we assessed the cost-effectiveness of treatment options for subacute EP re-

TABLE 4

Subsequent fertility^a according to hospital care pathway for subacute ectopic pregnancies (n = 517).

| Care pathway: ultrasound category by first-line treatment | Attempts to get pregnant | | | |
|---|--------------------------|----------------------|----------------------|--------------------------|
| | No attempt or IVF | No pregnancy | Miscarriage or EP | Intrauterine pregnancies |
| Conservative laparoscopy | | | | 123 (54.2; 47.7–60.7) |
| Diagnostic (n = 120) | 22 (18.3; 11.4–25.3) | 25 (25.5; 16.9–34.1) | 21 (21.4; 13.3–29.6) | 52 (53.1; 43.2–62.9) |
| Nondiagnostic (n = 169) | 40 (23.7; 17.3–30.1) | 29 (22.5; 15.3–29.7) | 29 (22.5; 15.3–29.7) | 71 (55.0; 46.5–63.6) |
| Radical laparoscopy | | | | 42 (44.2; 34.2–54.2) |
| Diagnostic (n = 72) | 30 (41.7; 30.3–53.1) | 16 (38.1; 23.4–52.8) | 9 (21.4; 9.0–33.8) | 17 (40.5) (25.6–55.3) |
| Nondiagnostic (n = 92) | 39 (42.4; 32.3–52.5) | 15 (28.3; 16.2–40.4) | 13 (24.5; 12.9–36.1) | 25 (47.2; 33.7–61.6) |
| Methotrexate: diagnostic (n = 64) | 18 (28.1; 17.1–39.1) | 10 (21.7; 9.8–33.7) | 10 (21.7; 9.8–33.7) | 26 (56.5; 42.2–70.9) |

Note: All data are number (%; 95% confidence interval).

^a Subsequent fertility assessed at the end of a 1-year period beginning during the 2 years after EP care.

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sulting from reproduction failure, regardless of whether the ultrasound examination was diagnostic or not. For each care pathway, the total costs associated with EP care for 1,000 hypothetical women (Table 3) and the expected number of intrauterine pregnancies after EP care (Table 4) were assessed, making it possible to compare care pathways in terms of costs and expected outcomes.

First-line treatment with methotrexate was cost-effective because much lower levels of resource allocation (one half to one third) were required to obtain an outcome in terms of intrauterine pregnancies at least as good as that obtained with conservative or radical laparoscopy. Total costs were similar for conservative and radical laparoscopy (about 3% difference), but subsequent fertility appeared to be better after conservative laparoscopy, suggesting that conservative laparoscopy may be cost-effective when compared with radical laparoscopy (salpingectomy). Similar results were obtained if mean costs per woman were considered rather than median costs, and a sensitivity analysis on costs had no effect on the findings.

DISCUSSION

This cost-effectiveness analysis dealt with the care pathways followed by women presenting EP in the real world of medical practice, rather than considering pairs of diagnostic or therapeutic alternatives for highly selected cases. It focused on the woman's subsequent fertility as the most relevant outcome, rather than on detection or complication rates, as generally used in previous studies (8–14). This study was also population based rather than university hospital or reference center based, and it distinguished acute EP from subacute EP, because care pathways clearly differ for these two types of EP.

By using this approach, we showed that the diagnostic or nondiagnostic nature of the initial ultrasound scan was the key component for medical decision-making concerning the care of subacute EP, because in practice, methotrexate treatment was only possible if the ultrasound scan was diagnostic. Our finding that about one in two ultrasound examinations is nondiagnostic therefore has important implications for the costs of subacute EP care. This high frequency of nondiagnostic ultrasound scans in routine practice is rarely considered in classical diagnostic studies (17) and was seldom discussed in previous studies comparing the cost-effectiveness of methotrexate and its alternatives. Otherwise, ultrasound results (diagnostic or not) had no effect on the costs of care and subsequent fertility associated with laparoscopy (whether radical or conservative). Care pathways for subacute EPs showed a gradual increase in the use of methotrexate with time, but the frequency of first-line treatment failure remained constant, suggesting that decision-making regarding first-line treatment depends more on medical choices between substitutable options than on clinical or technical constraints.

This study clearly shows that all conservative treatments, and methotrexate in particular, are cost-effective for subacute EP resulting from reproductive failure. Indeed, these conservative treatments gave better outcomes at equal or lower cost to the healthcare system. This finding, which was partly expected from cost studies indicating the superiority of methotrexate (6, 8, 10, 12, 18, 19) and from fertility studies indicating the superiority of all conservative treatments (20, 21), has clear consequences in terms of recommendations for practice. When future fertility is at stake (i.e., when EP results from a reproductive failure), in practice, conservative treatments should be preferred, with methotrexate used whenever possible, for subacute cases (about 80% of all cases) that have a positive diagnostic ultrasound (currently only about 50% of subacute cases). Radical treatment (salpingectomy) was found to be less costly than conservative laparoscopy in a Dutch study (22), but this was not the case in our study. Salpingectomy should henceforth have limited indications in the context of EP as a result of reproductive failure.

Several methodological aspects of this study merit discussion. We tried to maximize the relevance of our data to health systems outside France by collecting detailed data on resource use within and outside hospitals for each patient. This painstaking, prospective data collection procedure facilitates comparisons with similar studies performed at different times or in different health systems. The use of the national hospital-cost database provided estimates of costs representative of the situation throughout France, unlike methodologies based on charges or bills that are provided by hospital accounting departments (hospitals often have very different accounting practices and budget equilibrium constraints). However, our study has limitations. First, EP care in the French region of Auvergne cannot be considered to be representative of EP care worldwide, or even in Europe. However, its variety (shown in a previous study [23]) may be an advantage in this comparative cost-effectiveness study.

Second, there were missing data concerning medical costs and sick leave after hospitalization. It remains possible that medical costs differed in nature and quantity in a manner related to whether a woman returned her questionnaire on follow-up care. However, analysis of the available data showed that the impact of such differences would be negligible, given the much lower costs of ambulatory than of hospital care. Third, despite the large size of our sample, there were too few acute EP cases for a reliable cost-effectiveness analysis, and we therefore restricted our analysis to the women with subacute EP. Finally, our study was purely observational. However, randomized trials for all EP care pathways are difficult to perform, or even to advocate, at the regional level. Population-based studies, such as those based on morbidity registers, have been shown to be complementary to randomized controlled trials for assessing therapeutic or health interventions (24).

In summary, conservative treatments, and methotrexate in particular, appeared to be cost-effective for EP cases in which the preservation of fertility was important. Efforts should be made to decrease the proportion of nondiagnostic ultrasounds, which prevent the use of methotrexate and reduce the cost-effectiveness of care.

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