Introduction and provision of medical abortion:
A tale of two countries, in which technology is necessary but not sufficient

Introduction et utilisation de l'avortement médicamenteux:
Une histoire dans deux pays, qui montre que la technologie est nécessaire mais pas suffisante

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BACKGROUND

SITUATION

Le développement d'une technologie qui a permis de faire des avortements précoces en utilisant des médicaments est une des avancées les plus importantes de ces dernières années en matière de santé reproductive. La diffusion de la méthode a connu des différences notables dans les pays. Les différences dans l'introduction de la méthode, si l'on compare la France et les Etats-Unis, montrent que celles-ci furent liées à des différences dans les pratiques sociales et économiques d'un pays à l'autre mais aussi au contexte politique, au système de santé et à la pratique de la médecine.

Un avortement médicamenteux est une interruption de grossesse induite par des médicaments et ne nécessitant pas de geste chirurgical. Les médicaments utilisés sont la mifépristone (RU 486) associée à une prostaglandine. La mifépristone est un stéroïde de synthèse ayant des propriétés anti- progestérone puisqu'elle se lie fortement aux récepteurs de la progestérone sans les activer. La forte affinité (cinq fois plus forte que la progestérone elle-même) de cette molécule en fait un abortif très puissant. La prostaglandine qui lui est associée le plus souvent est le misoprostol. Cette molécule a pour effet d'augmenter la contractilité de l'utérus préparée au préalable par l'action de la mifépristone. Cette association des deux médicaments, jusqu'à 63 jours d'aménorrhée, induit une interruption de grossesse dans 92 à 98% des cas. Le protocole qui a reçu l'autorisation de mise sur le marché (AMM) en France mais aussi en Europe et aux USA est 600mg de mifépristone (3 comprimés) suivi 36 à 48 h plus tard par 400µg de misoprostol par voie orale pour une grossesse de moins de 7 semaines d'aménorrhée.

AVORTEMENT MEDICAMENTEUX EN FRANCE

MEDICAL ABORTION IN FRANCE

L'avortement médicamenteux constitue une alternative très efficace et sure à l'avortement chirurgical. La France fut le premier pays en 1989 (avec la Chine) à commercialiser la méthode. L'introduction de cette méthode et sa diffusion ne se firent pas sans difficulté alors même que l'interruption de grossesse était légalisée depuis 1975 et socialement admise.

L'histoire de l'avortement médicamenteux [1,2] a débuté en 1980 avec la découverte d'une anti hormone le RU 486 [1], par les chercheurs du laboratoire Roussel Uclaf. Cette nouvelle classe de médicaments a d'abord soulevé peu d'intérêt de la part des chercheurs puis, quand il est apparu que la molécule était abortive, la crainte des implications politiques en a ralenti le développement. Dès le début des études cliniques, à tous les niveaux du laboratoire et en particulier à celui du directoire du laboratoire Hoechst[2], il y a eu une forte opposition à poursuivre les recherches. C'est grâce à l'insistance du Professeur Baulieu et de quelques chercheurs de Roussel Uclaf que les essais ont pu se poursuivre et que le développement de la molécule a été possible. Les toutes premières études cliniques ont été faites en Suisse en 1982 puis en France à partir de 1983 dans les centres d'Interruption de grossesse des hôpitaux publiques. C'est en 1988 que la mifépristone sous le nom de Mifegyne® obtint l'autorisation de mise sur le marché. Peu de temps avant le lancement du produit, Roussel Uclaf, devant la menace de boycott international de ses autres produits, orchestrée par les mouvements anti-avortements, a alors annoncé son retrait du marché.

[1] Le RU 486 est la 34486eme molécule découverte par la laboratoire Roussel Uclaf.
[2] Le laboratoire Roussel Uclaf était lié depuis les années soixante dix au laboratoire allemand Hoechst

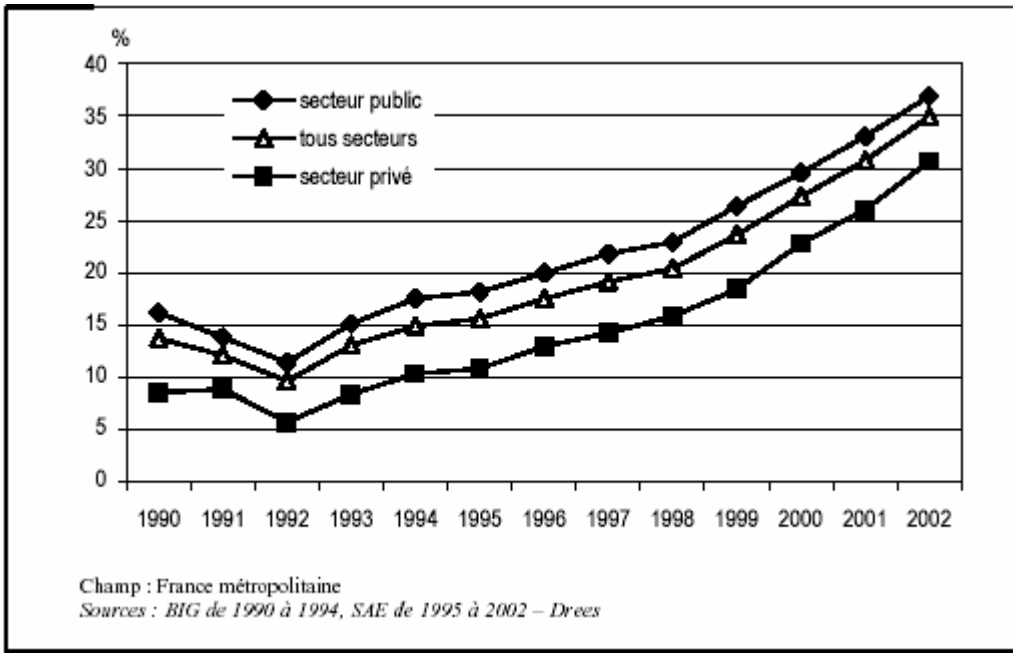
Les mouvements féministes se sont alors mobilisés et des protestations se sont élevées de la part de personnalités politiques conscientes de l'amélioration médicale que représentait ce produit. Claude Evin, Ministre de la Santé, considérant que « le RU 486 est la propriété morale des femmes » a alors, comme la loi le lui autorise contraint le laboratoire à revenir sur sa décision et par un arrêté du 28-12-1988 en a réglementé l'utilisation[3]. Plus tard, le président du groupe Hoechst considérant que ce produit n'était pas compatible avec l'éthique du laboratoire décida rapidement d'en abandonner la fabrication et la commercialisation au Dr Sakiz, chercheur et président du Directoire de Roussel Uclaf ; celui-ci créa alors en 1992 le laboratoire Exelgyn qui depuis en assure la diffusion.

Pendant les 10 premières années, bien que satisfaits de cette nouvelle technique, les prescripteurs de la méthode restèrent assez isolés, ne cherchant pas à modifier le protocole initial malgré de nombreuses études montrant que l'on pouvait le simplifier. Ce n'est qu'en 2001, quand sont parues les recommandations de l'Agence Nationale d'Accréditation et d'Evaluation Scientifique (ANAES)[3] que les prescripteurs ont commencé à modifier leur pratique en diminuant la dose de mifépristone utilisé et en le proposant « à domicile » . Il est vrai que la loi de 1975 sur l'avortement n'autorisait celui ci que dans les établissements de santé ce qui de fait obligeait à cette hospitalisation de trois heures non justifiés scientifiquement. Ainsi, après 15 ans d'une lente progression (Fig 1), les dernières années ont vu une augmentation notable du nombre des IVG médicamenteuses. En 2002, 35 % des avortements ont été des avortements médicamenteux soit 2/3 des avortements faits avant 7 SA [4]. Les IVG médicamenteuses sont

[3] Les conditions de remboursement ont été fixées par un arrêté du 20 février 1990 dans les mêmes conditions que pour les avortements chirurgicaux.

plus fréquentes dans le secteur public que dans le secteur privé mais l'augmentation enregistrée au cours des dernières années portent sur les deux secteurs. En France, il n'existe pas de secteur privé associatif pour prendre en charge les IVG. Celles-ci sont donc faites dans les services de gynécologie obstétrique du secteur privé ou du secteur publique.

Figure 1 : Evolution du nombre d'IVG médicamenteuses par secteur depuis 1990.



Villain A. Les interruptions volontaires de grossesse en 2002. Etudes et résultats, DREES, n°348. Octobre 2004.

La diffusion de la méthode un peu partout dans le monde et les nombreuses publications en particuliers américaines ont refaits parler de l'IVG médicamenteuse et ont accéléré la nécessaire modification d'une loi sur l'avortement qui datait de 1975 et ne correspondait plus aux besoins, aux pratiques sociales et aux innovations scientifiques de ces dernières années. Le 17 avril 2001, les députés ont adopté en deuxième lecture, une nouvelle loi sur l'interruption de grossesse et la

contraception[4] autorisant l'IVG médicamenteuse hors des établissements de santé. Dans le cadre d'un réseau ville/hôpital, les médecins, dans leur cabinet privé, peuvent maintenant proposer aux femmes qui en font la demande une IVG médicamenteuse, l'hôpital restant le recours en cas de complications ou d'échecs. Les décrets et circulaires qui permettent la mise en place de ce dispositif n'ont été promulgué qu'en juillet et novembre 2004. En effet, cette circulaire précise les devoirs et obligations du médecin mais aussi ceux de l'hôpital auquel le médecin doit être affilié par une convention. Elle spécifie, ce qui est plus inhabituel, le protocole (doses et produits) à utiliser et le nombre de consultations qui doit être fait. En quittant l'hôpital, l'avortement médicamenteux échappe ainsi au contrôle institutionnel mais reste très strictement encadré. Un certain nombre d'éléments ont caractérisé l'introduction et l'utilisation de cette nouvelle méthode d'interruption de grossesse en France.

La politisation

La commercialisation lors de la mise sur le marché en 1989 fut très politisée. Le progrès scientifique que représentait cette méthode pour la santé des femmes a été occulté par la nature abortive de la molécule et la crainte d'une banalisation de l'avortement. De nouveau en 2001, quand se sont discutées les modifications d'une nouvelle loi sur la contraception et l'avortement, le spectre de la banalisation de l'avortement par la méthode médicamenteuse a resurgi. Cependant, même si les mouvements anti-avortements ont parfois été violents et ont trouvé un certain écho parmi quelques personnalités politiques, l'avortement est une pratique sociale tolérée dans la société française et n'est plus un enjeu politique aussi violent qu'aux USA. De plus, l'intervention de l'état a même été déterminante, forçant le laboratoire à commercialiser le

[4] Texte adopté n° 655 « petite loi » Session Ordinaire de 2000-2001-- 17 Avril 2001

RU 486 en 1989 et en en élargissant l'utilisation en 2001. L'agrément de l'état donné à ces pratiques exige cependant le respect de procédures de contrôle et un encadrement très strict de l'avortement médicamenteux limitant ainsi une diffusion plus large et ne permettant pas aussi rapidement qu'aux USA l'adoption d'avancées scientifiques.

Absence de recherche et peu de formations organisées

L'absence de recherche, hors celles du début, sur ce sujet s'explique par le faible intérêt manifesté par les médecins hospitalo-universitaires pour cette molécule abortive, essentiellement utilisée dans les centres d'IVG, souvent par des militants, peu habitués à publier. De plus, le laboratoire pharmaceutique français (Exelgyn) qui commercialise la mifépristone n'a pas souhaité soutenir la recherche sur cette molécule. Ceci, alors que les Etats-Unis, avant même la commercialisation dans leur pays, amélioraient et simplifiaient le protocole initial. Cette absence de grandes études françaises explique peut-être aussi le maintien en France du protocole initial dont l'AMM n'a certes pas changé, mais qui n'est plus scientifiquement validé. De ce fait, il existe ainsi actuellement une certaine contradiction entre les recommandations de l'ANAES de 2001 qui proposait un protocole plus simple (un seul comprimé de mifépristone et l'absence d'hospitalisation) et la dernière circulaire de 2004 permettant la mise en place de l'IVG médicamenteuse dans les cabinets privés et qui oblige à utiliser uniquement le protocole ayant l'AMM.

Si les congrès français de gynécologie obstétrique ont parfois rapporté dans leur programme quelques expériences françaises de la méthode, il n'y a pas eu de formation plus spécifiquement organisée sur ce sujet puisque les médecins ne travaillant pas à l'hôpital ne pouvaient proposer la

méthode à leurs patientes. La nouvelle loi va modifier cet état de choses en obligeant les centres d'IVG de former les médecins signataires des conventions.

L'intégration dans le système de santé

L'intégration immédiate dans le système de santé et la prise en charge financière à un tarif équivalent à l'IVG chirurgicale (environ 200€ avec un remboursement à 80%) a rendu la méthode accessible financièrement à toutes, le prix ne pouvant être considéré comme un critère de choix. Le tarif IVG, considéré comme relativement bas, est certes peu incitatif pour les médecins et explique le désintérêt du secteur privé pour la méthode. La diffusion même dans le secteur public a été très variable d'une région à une autre. Elle a été fortement dépendante des connaissances et de l'acceptation des équipes en place.

Malgré des conditions relativement favorables, la diffusion fut donc relativement lente en France. (Fig 1). Ceci pourrait être liée d'une part à la réticence des médecins à adopter de nouvelles techniques mais aussi au fait que la méthode a surtout été proposée dans certains centres d'IVG des hôpitaux publiques avec une moindre diffusion dans les hôpitaux privés ou pourtant près de la moitié des IVG étaient faites (4). Les différents rapports sur l'IVG en France [5,6] avaient clairement montré que peu d'établissement proposait le choix de la méthode. . Par ailleurs, la loi sur l'IVG qui oblige à un délai de réflexion d'une semaine entre la première demande et l'intervention place hors délai pour la méthode un certain nombre de femmes qui pourtant souhaiteraient en bénéficier. Un nouveau contexte international et des études nombreuses ayant confirmé l'efficacité et la sécurité de la méthode devraient permettre de rassurer les prescripteurs d'autant que la demande des femmes est de plus en plus importante. Les modifications de la loi sur l'IVG autorisant les IVG médicamenteuses hors des

établissements de santé devraient augmenter de façon notable le nombre d'IVG médicamenteuse faite en France. Tout va maintenant dépendre de la mise en application des nouveaux dispositifs. Celui-ci n'étant effectivement en place que depuis novembre 2004, il est encore trop tôt pour en évaluer l'impact.

MEDICAL ABORTION IN THE US

The unusual and very particular circumstances of the registration and introduction of mifepristone in the United States shaped the way medical abortion is offered and used in the US. A drug registration and introduction process that was not controlled by commercial entities in the usual way combined with the special norms of American medical practice (physician autonomy, patient advocacy, and lack of universal insurance coverage) to create very singular practices in the provision of medical abortion. Initially, American abortion politics terrified all potential commercial sponsors of the product, RU-486 (mifepristone). As a result, non-governmental organizations and private foundations took on a central role in facilitating mifepristone approval in the United States. Throughout the approval process, a network of professional, women's health and advocacy organizations sought to increase public awareness about and interest in the method. These groups effectively took on the roles normally played by pharmaceutical companies during a drug's approval and introduction. Since drug approval, this network has developed innovative training curricula, guidelines, and interactive information sources that have facilitated the spread of the method among abortion providers. At the same time, the widespread normative professional medical practice of off-label drug use in the US has fostered the development of innovative practice regimens that make the method more acceptable to women

and providers. As a result, five years after drug approval, the method is available in an increasing number of abortion and family planning clinics throughout the US.

Since the early 1980s, the American media has taken an active interest in the discovery and research related to the "French abortion pill," RU-486. Research developments were regularly covered in American medical journals and daily newspapers, prompting both academic interest and popular speculation about the political and social impact of "the abortion pill."
The publication of results from a French clinical trial of mifepristone in the New England Journal [7] was accompanied by an editorial in that journal heralding the promise of the drug and warning of its potentially "enormous impact on society" and American medicine [8]. Politicians also weighed in on the implications of the scientific development, and the US fascination with the "French pill" reflected in a feature article on Dr. Etienne Emile Baulieu who researched and promoted the drug with a team at Roussel Uclaf, the French pharmaceutical company, in one of the prominent national newspapers. [9] Particularly after the bombings of abortion clinics by members of Operation Rescue in 1984, even the prospect of an abortion medication provoked passionate responses from advocates on both sides of the issue.

This interest in the "French pill" also translated into active opposition among anti-abortion groups on both sides of the Atlantic. In early 1988, the National Right to Life Committee in the United States wrote a letter to France's Ambassador to the United States urging the French government to deny permission to Roussel to market the drug. [10] Roussel Uclaf's decision to halt distribution of mifepristone in France shortly after the drug was approved (see above) received front page coverage in leading US newspapers and elicited support from abortion

opponents and condemnation from pro-choice groups, family planning advocates and sympathetic politicians in Washington. Although Roussel later resumed distribution in France, the company refused to submit an application for authorization to market and distribute the drug in the United States

Indeed, abortion politics ensured that throughout the 1990s mifepristone, while approved for use in France, the United Kingdom and, later, Sweden, could not be obtained in the US for use outside of clinical trials. Roussel was reluctant to enter the market for fear of the perceived political pressures and insurance risk associated with marketing an abortifacient in the United States [1]. American pharmaceutical companies were also not eager to make the drug available. The Upjohn Co had tested the drug in its labs but later discontinued fertility-control research because of the difficulties of bringing a product a profitable product to market. In an interview with the Washington Post in 1986, Dr. Jacob Stucki, the vice president for pharmaceutical research, explained, "FDA standards are so high, and the chances of getting something approved are so low, it just isn't worth it."[9]

The federal government did little to allay the pharmaceutical industry's fears. In June 1989, the United States Food and Drug Administration (USFDA) banned the importation of mifepristone for personal use. [11] Historically, the USFDA has allowed for the importation of small amounts of drugs for the personal use of patients, provided that they do not pose unreasonable or significant safety risks and that they will not be commercialized. However, the USFDA refused to allow the importation of mifepristone for personal use on the grounds that the drug presented a "threat to public health" and that the availability of the drug overseas might create a demand in

the US and lead to “unsupervised use and/or clandestine distribution.” [11] Needless to say, this “import alert” was widely interpreted as a political act.

The USFDA decision prompted a public outcry from professional medical organizations, politicians and abortion activists. While many were concerned about government efforts to curtail abortion rights, the debate over mifepristone also became symbolic of broader concerns about the role of the federal government in regulating scientific research. In June 1990, the American Medical Association passed a resolution supporting “the legal availability of RU-486 for appropriate research and, if indicated, clinical practice”, in part, because they feared the creation of a “black market” for the drug if it was not introduced through conventional channels. The chairman of the association committee, Dr. Charles Sherman explained, “The abortion issue, pro and con, should not interfere with our ability of conduct all kinds of investigations for all kinds of problems.” [12]

National and regional politicians also took an interest in the implications of the import alert for scientific research in the US. In November 1990, Congressman Ron Wyden held hearings before the Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business in the House of Representatives to discuss how the import alert had hindered research on non-abortion indications, including breast cancer. In February 1991, the American Association for the Advancement of Science (AAAS) supported the testing and use of RU 486, and in May 1991 the state of New Hampshire issued a state resolution urging the commencement of clinical trials.

In the meantime, abortion activists adopted less conventional strategies to facilitate the removal of the import alert. In July 1992, the Feminist Majority Foundation and Larry Lader of the Abortion Rights Mobilization group sought to bring increased attention to the issue. Leona Benten, a New York socialite, returned from Europe with mifepristone pills. Customs officials seized the drug. [13] While the Supreme Court refused to order Customs to overturn the import ban, the U.S. District Court that examined the "import alert" later concluded that, "[T]he decision to ban the drug was based not from any bona fide concern for the safety of users of the drug, but on political considerations having no place in USFDA decisions on health and safety." [14] More importantly, the publicity stunt generated media coverage of the issue and solidified support among pro-choice groups.

Ultimately, a change in the executive office opened the door for the introduction of mifepristone in the US. Shortly after assuming office, President Clinton signed an executive order directing Donna Shalala, the head of the department of Health and Human Services (HHS) to determine whether the current ban on mifepristone was justified and to rescind the ban if it had no basis. He also ordered the HHS to explore the propriety of promoting testing in the United States as well as the possibility of licensing and manufacturing according to the standards which govern all other drugs reviewed by the USFDA. The order was accompanied by requests to rescind the moratorium on federal funding for stem cell research and to suspend the Title X family planning regulations also known as the "gag rule". [15] Meanwhile, USFDA Commissioner David Kessler, in an unprecedented approach by a US government official to a pharmaceutical company, also wrote to Roussel Uclaf encouraging the company to submit an application to license RU 486 in the US. Later that year, a National Academy of Sciences panel's conclusions

reinforced the scientific promise of the drug and held that the mifepristone and other drugs in its class should be studied extensively as possible treatments for a wide variety of indications. [16]

Several years earlier, in 1984, Roussel had signed contracts with the both World Health Organization in Geneva and the Population Council, a non-governmental research organization in New York, allowing both organizations to conduct research and to facilitate the drug's introduction into developing countries. Starting in 1985, the company initiated several studies in the US in collaboration with the Population Council and the National Institutes of Health. Most studies focused on the pharmacological characteristics of the drug, but others tested its use for pregnancy termination and obstetrical indications. [1] On May 16, 1994, Roussel Uclaf concluded negotiations with the Population Council by agreeing to assign the US patent rights for RU 486 (mifepristone) without remuneration to the non-profit organization.

In October 1994, after having received the patent rights for mifepristone, the Council started a trial of mifepristone for early pregnancy termination enrolling over 2100 women. Thousands of women called to volunteer after Planned Parenthood clinics in Houston and five other cities announced they would take part in the trials. [17] After the conclusion of the trials, the Council submitted a New Drug Application (NDA) to the USFDA, and the USFDA issued a subsequent "approvable letter" in 1996. The letter specified that the clinical evidence showed that the drug was approvable but that certain issues related to manufacture and distribution systems needed to be worked out. The Council encountered various difficulties in identifying a manufacturer, but ultimately granted Danco Laboratories an exclusive license for marketing and distribution of mifepristone.

In September 2000, Danco was granted FDA approval for marketing and distributing mifepristone (marketed under the trade name Mifeprex®) in the US. The registered label specifies the use of 600 mg mifepristone and 400 mcg oral misoprostol for the termination of pregnancies up to 49 days since the last menstrual period (LMP). The USFDA worked with the sponsor and distributor to develop a restricted distribution scheme. Consequently, although mifepristone is a prescription drug, it is not available to the public through licensed pharmacies. It can be supplied directly to patients only by licensed physicians who sign and return a Prescriber's Agreement to the distributor of the drug. The Prescriber's Agreement and drug label specify that a physician must be able to date the age of gestation (although the method used is not specified), to diagnose ectopic pregnancy and to provide or arrange for referral for surgical aspiration if needed. All capacities are self-certified, however, allowing for some flexibility in where and by whom the method can be provided.

The long delay in mifepristone approval led to several important developments that would shape research on mifepristone as well as the provision of the method once approved. First, frustrated with the delays in the availability of mifepristone, abortion activists took matters into their own hands. In February 1993, Larry Lader announced that the Peking Union Medical College had given the Abortion Rights Mobilization (ARM) group permission to test the Chinese copy of mifepristone. Several months later, Lader declared that the mifepristone compound had been replicated by scientists in a laboratory in New York State. In 1996, Lader obtained USFDA approval to use ARM's version of the drug in research trials in several sites around the country. According to federal law, groups are allowed to copy patented drugs for research use as long as

they do not offer them commercially. In 1997, ARM obtained additional financing from the John Merck Fund to expand the trial to additional sites in New York, Texas, Maryland and Florida. [18] This network of highly committed researchers would continue to develop innovative regimens that have made the method more acceptable to women and providers.

Second, without access to mifepristone, several American researchers explored the use of methotrexate, a widely used cancer drug, in combination with misoprostol, a drug marketed for gastric ulcers, for the induction of abortion. [19-22] The results of these early studies came to inform subsequent clinical studies of mifepristone [23] and the clinical use of mifepristone medical abortion after drug approval in 2000. Creinin and colleagues showed that vaginal misoprostol was more effective than oral misoprostol to induce abortion. [24] Hausknecht demonstrated that medical abortion could be performed up to 63 days LMP and that self-administration of vaginal misoprostol after methotrexate is safe, effective and acceptable to women [20]. Other researchers validated these findings. [21]

Today, while the approved regimen remains 600 mg mifepristone followed by in-clinic use of 400 mcg oral misoprostol to 49 days LMP, most US clinicians use 200 mg mifepristone and 800 micrograms vaginal misoprostol administered by the patient at home to 63 days LMP. The Planned Parenthood Federation of American (PPFA) allows its affiliates to use 200 mg of mifepristone, with additional consent, and also for a woman to self-administer the misoprostol at home. Also, the National Abortion Federation (NAF) advises providers in its protocol that the reduced mifepristone dose is as effective as the 600 mg dose in a regimen with 400 micrograms misoprostol orally when used up to 49 days LMP.

While early clinical research informed mifepristone use after approval in 2000, the profile of abortion seekers and the existing geography of abortion services have shaped the demand for, availability and use of the method in the US. Abortion is one of the most common surgical procedures in the United States. Each year about 1.3 million pregnancies are terminated by abortion in the United States and more than one-fifth of all pregnancies end in abortion. [25] Most women seeking an abortion in the US come early in their pregnancy, making medical abortion a realistic alternative for many. Of all abortions in 2001, 59.1 percent occur in the first eight weeks of pregnancy and at least 10 percent in the ninth week [26] making more than two thirds of US abortion potentially eligible for mifepristone as currently provided.

Information on the extent of use of mifepristone for early pregnancy termination is based largely on sales data from Danco Pharmaceuticals, the sole distributor of mifepristone in the United States. In the first 18 months of use from November 2000 to May 31, 2002, the company estimated that approximately 80,000 women received mifepristone for early abortion. [27] The total number of mifepristone medical abortions has increased substantially each year. By April 2005, more than 450,000 women had used Mifeprex®. According to estimates from Danco Laboratories, up to 18 percent of eligible abortions are now performed using mifepristone [28]. Use of mifepristone in the United States has been associated with high rates of success (94-77 percent) and a low rate of adverse events (0.17 percent adverse events in the first eighteen months of use. [27].

In 2000, clinics made up almost one-half (46 percent) of all US abortion providers, and more than one half of these clinics (or 25 percent of all providers) were specialized abortion clinics, defined as those where at least half of patient visits are for abortion services. [25] In 2000, most abortions (93 percent) were performed in clinics. [25] The use of mifepristone abortion has been informed by these service delivery patterns. In early 2001, six months after the approval of mifepristone, about half of clinics offering abortion services provided early medical abortion, as did one in five hospital abortion providers [25]. Today, mifepristone sales to all types of abortion providers have continued to grow with sales to clinics still representing the large majority (89 percent) of all sales [26].

The Planned Parenthood Federation closely monitors the use of mifepristone in their affiliates and has documented the spread of the method in Planned Parenthood clinics since approval. Since March 2002, the number of clinics offering the service has nearly tripled (from 73 clinics in 2001 to 231 clinics in 2004), including 75 sites that had not previously offered abortion services. [29] Between January 2001 and December 2004, over 130,000 women had abortions using mifepristone and misoprostol at Planned Parenthood clinics in the US. In the fourth quarter of 2004, 25 percent of first-trimester patients, or 38 percent of eligible patients, chose medical abortion. [29] Indeed, medical abortion has come to represent an increasing percent of first trimester procedures.

In the US, a large majority of women (74%) pay for their abortions with their own money or with funds they obtain from their partner, family or others. [30] Although the federal government, through its sponsorship of Medicaid programs in the states, may pay for abortion

(although only in cases of rape, incest and life endangerment), only 16 states cover abortions under their Medicaid programs, either voluntarily or under court order. [30] While there are significant regional differences in the levels of private or Medicaid funding for abortion services, most abortion costs are paid out-of-pocket. A recent survey found that only 1% of medical abortion clients used insurance to cover their abortions and many (44%) did not know if their insurance would cover their abortions or not. [31]

The insurance situation in the US has important implications for the use and accessibility of mifepristone. On the one hand, because few insurance providers cover the procedure, insurance companies exert little influence over practice patterns or standards of care compared to other surgical or reproductive health procedures. As a result, clinics and providers have been free to develop innovative service models for provision of the service that ultimately may have reduced the overall cost of the procedure. On the other hand, the price of the procedure may vary widely. Studies have found that the adjusted cost of providing medical abortion care varies significantly, depending upon the practice model used (from $252-$460 per abortion, median $351). [31] Consequently, the method may be more or less accessible or a more or less attractive alternative to surgical abortion depending upon the practice and pricing model in place.

The course of mifepristone registration in the US reinvigorated a committed network of healthcare providers, abortion activists, advocacy and non-governmental organizations. This network has facilitated the introduction and use of mifepristone resulting in a rapid increase in the use of the method and the development of innovative regimens and practice patterns. Despite these significant gains, controversy surrounding the drug is not likely to diminish and

may inhibit women's access to the method in the future. In January 2003, a bill was re-introduced in the House and Senate which would legislatively override the USFDA's approval of mifepristone and would require an entirely new, additional "review" of the drug's approval. The bill is moving slowly, and the debate surrounding the legislation will likely be colored by other controversies regarding the USFDA's safety review and drug approval processes. The political situation may be further complicated by the sale of mifepristone and misoprostol over the internet and the movement of drugs across borders and, much to the chagrin of abortion opponents, the drug's promise for the treatment of a variety of non-obstetric indications.

DISCUSSION

The development of a method to provide early abortion using drugs instead of surgery has been called a landmark advance in reproductive health for women. Although the technology flowed from a single source (the French company, Roussel-Uclaf), the evolution of services surrounding its use has differed markedly in different national environments. Variations in drug registration and regulatory processes, pharmaceutical companies, medical practice, abortion service provision and public opinion have shaped access to medical abortion. The introduction of the technology has been deemed a "success" in each country, and the growing utilization of the drug can be tracked in each place.

The "abortion pill" (RU486) was first invented, registered and marketed in France and became a symbol of the advantages European women held over American women in areas of sexuality, reproductive health, and abortion provision. Nonetheless, the development and registration of this product was not without controversy even in France. Despite the fact that the technology

has taken hold in both countries, there are marked differences in the way in which services are provided.

Despite the more usual drug registration process in France, the strong centralization of medical authority and government regulation of medical practice in that country has meant that the method is much less widely used than it could be and that innovation with the drug has been largely left to other actors in other countries until the present. In France, until recently, medical abortion services had to be provided within hospitals strictly according to the registered regimen (use only up to 49 days LMP gestational age, ingestion of 3 tablets of mifepristone at a hospital visit followed 48 hours later by 2 orally administered tablets of misoprostol during another visit to the hospital, with a final visit for follow up about two weeks later). Because of the overarching French abortion law, all women opting for this or for surgical abortion in the first trimester were forced to observe a waiting period from the time they indicated the request for an abortion until the procedure could actually take place, meaning that some women could exceed the gestational age limit before they could get access to the method.

In the US, the process of registration of mifepristone was incredibly prolonged due to the insertion of political issues into a normal drug registration process. The complications that arose from this very unusual situation meant that a non-profit organization had to shepherd the introduction of the drug with the aid of the advocacy community. This alliance allowed much more access of women's health experts and advocates to the decision-making aspects of drug introduction.

At the same time, the prolonged interval between awareness of the technology and official introduction of the drug led innovators in the US medical community to begin to experiment with new approaches to service delivery even before drug registration. These innovations in services had been absent from the service delivery environment in the three European countries that were already providing the method. In France, the strong role of the state served to provide a clearer path to drug introduction but, also, government participation in medical care made the rules of service delivery stricter, services more uniform and creativity less likely. The legal framework of both drug use and abortion service delivery in the U.S. helps to explain the unique (and ultimately much more woman-friendly) service delivery models that have evolved there. Despite the preponderance of "off-label" use in the U.S., the method has served over 450,000 women with extraordinarily high success rates and low complication rates. Indeed, the feasibility of doing the local clinical research on which US innovations for the method are based was enhanced by the concentration of abortion care, dictated, in part, by the political and economic difficulties shaping the service delivery system for voluntary pregnancy termination in that country.

Although the technology of medical abortion started out the same for both countries, in the US, innovations in medical practice were made possible by an unorthodox drug registration situation, the participation of the women's health advocacy community in normal pharmaceutical tasks, the less centralized medical practices in the US and the comfort of US physicians with off-label use of drugs. On the other hand, none of this innovation would have been possible without the willingness of French science and industry to engage in abortion research. The attitudes of the French government and public were crucial in allowing registration of an abortion technology without resort to the automatic exceptionalism that has characterized all aspects of abortion

research, services, and discussion in the US. Indeed, at bottom, the story of mifepristone in both countries demonstrates that there is more than one way to arrive at public diffusion of new technologies and that new ideas need to find their roots in local soil before they are adapted and adopted widely. On the other hand, one caution for the pubic health community is that proof of safety, efficacy, and patient acceptability are in themselves not enough to assure successful introduction and widespread use of medical innovations.

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