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PATIENT CENTERED FAMILY PLANNING CARE

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PATIENT CENTERED FAMILY PLANNING CARE

BY

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THESIS

Submitted in Partial Fulfillment of the
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PATIENT CENTERED FAMILY PLANNING CARE

By

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Introduction

The Institute of Medicine defines six important domains of health care quality: safety, efficacy, timeliness, efficiency, equitable delivery and patient-centeredness. Quality family planning care aims to provide individuals with the tools needed to engage in healthy and satisfying sex lives while planning and spacing pregnancies to achieve desired family size. The field of family planning strongly relies on the domain of patient-centeredness as individual values and preferences guide clinical care. Yet large gaps in knowledge exist in understanding how to improve patients' clinical experience. This hybrid thesis posits avenues for improving the quality and patient-centeredness of clinical care.

Quality care is meaningless if the public cannot access care. Numerous barriers to health care exist in the US for many. Education about our bodies, confusing media messaging about sex, cultural attitudes about sex and young parenting, conflation of contraception with abortion in politics and Catholic hospital mergers create barriers to access to care.

On the other hand, a facilitator of access is an increase in comfort among providers and patients with long acting reversible contraceptives or LARC. Encompassing intrauterine devices (IUDs) and implants, LARC methods are highly effective contraceptives that do not require ongoing adherence. These methods are exploding in popularity, but can be difficult to obtain due to cost or difficulty obtaining an appointment with a trained provider.

Extended duration of contraceptive implants may allow better contraceptive coverage as women navigate access barriers. Additionally, IUDs can be painful to place in the office setting. An anesthetic medication allowing an IUD to be placed with less discomfort may empower women who might not otherwise feel comfortable with placement of this method. Nitrous oxide is an inhaled gas that has been used in a number of settings in medicine. As a novel agent for painful outpatient gynecologic procedures, it provides the unique benefit of rapid clearance, potentially allowing a woman to obtain an IUD under this rapidly reversible anesthesia and return to her daily activities. Nitrous oxide may also preserve privacy, as other anesthetic options often require that a woman have a driver following the appointment. Privacy is particularly important in provision of abortion care.

These included chapters identify opportunities for the health care community to improve quality per the Institute of Medicine's domains.

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CHAPTER 1
Family Planning American Style Redux: Unintended Pregnancy Improves, Barriers
Remain

Because this is America. You're supposed to pretend that you don't notice certain things.

—Chimamanda Ngozi Adichi, *Americanah*

INTRODUCTION

The rate of unintended pregnancy in the United States had been stagnant for several decades, hovering around 50% to 51% of all pregnancies. That rate has finally and definitively decreased. In the most recent cycle of the National Survey of Family Growth (NSFG), a survey reported periodically by the Centers for Disease Control and Prevention (CDC), the rate fell to 45% in 2011, compared with 51% in 2008 (1).

Rates of unintended teenage pregnancies, births, and abortions also have fallen. From 2006 to 2014, teenage birth rates decreased 41% (from 41.1 to 24.2 per 1000 teenagers) (Fig. 1) (2). Reductions have occurred across all ethnicities, including African American, Hispanic, and non-Hispanic white teenagers. The largest declines occurred in Hispanic teenagers, followed by African American and non-Hispanic white teenagers.

Facilitating these changes are concerted efforts to address the social determinants of teenage pregnancy, including review of community-level reproductive health data by stakeholders, greater access to reproductive health services, and availability of teenager-focused and culturally competent health education materials. Additionally, increases in planned pregnancies are caused by improved access to and use of long-acting reversible contraceptive (LARC) methods, top tier in contraceptive effectiveness (1).

Although rates of unintended pregnancy, teenage pregnancy, and abortion have dropped dramatically, they remain higher than those for comparable countries in Western

European countries. US rates are approximately twice those of France and Sweden (3). Moreover, despite improvement, disparities persist in unintended and teenage pregnancy among certain racial and ethnic groups. Black and Hispanic teenagers had higher pregnancy rates (93 and 74 per 1000 teenagers) than non-Hispanic white teenagers (35 per 1000 teenagers) (2).

The larger picture goes beyond sexual health to broader social determinants. A recent literature review revealed that socioeconomic factors at the individual and community level, unrelated to sexual health, have a profound effect on teenage pregnancy (4). Such factors as underemployment, inadequate income and education, and growing up in a disadvantaged neighborhood at the low end of income inequality remind us that solutions to teenage and unintended pregnancy require wide-ranging social change with a focus on equity across the various domains.

This article discusses barriers to reducing unintended pregnancy, focusing on societal obstacles to sexual health. Numerous factors may explain the higher rate in the United States, including inadequate sexual education for adolescents, confusing messages from the media, cultural attitudes about sex and young parenting, conflation of contraception with abortion, burdensome contraceptive dispensing practices, and

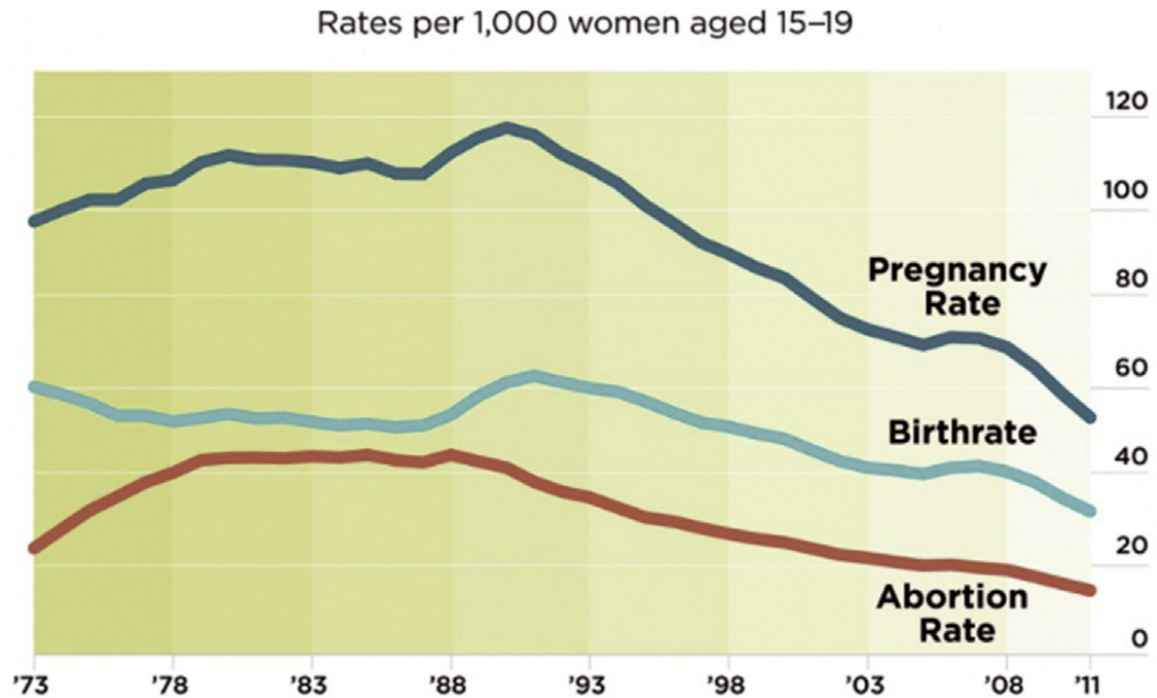


Fig. 1. US teenage pregnancy, birth, and abortion rates 1973 to 2011. (From Guttmacher Institute. U.S. teen pregnancy, birth and abortion rates reached historic lows in 2011. Infographic. New York: Guttmacher Institute; 2016. Available at: <https://www.guttmacher.org/infographic/2016/us-teen-pregnancy-birth-and-abortion-rates-reached-historic-lows-2011>; with permission.)

reduced access to health care caused by lack of insurance or hospital mergers. Yet several facilitators can counteract these factors, expanding access to reproductive health care. Local communities and society at large should pursue progressive strategies as a public health priority.

INFLUENCE OF SEXUALITY EDUCATION ON UNINTENDED PREGNANCY

Sexuality education remains a battleground. Beginning in the 1980s and increasing substantially with welfare reform in 1996, significant federal funding promoted abstinence-only-until-marriage education. The federal/state matching program mandated that states receiving federal funding would provide sexuality education that met strict criteria, complying with an eight-item definition of abstinence-only education.

The goal of this curriculum is to persuade young people to abstain from sexual activity. It teaches that abstinence is the only certain way to avoid pregnancy and sexually transmitted infections; that sexual activity outside marriage is likely to have harmful psychological and physical effects; and that a mutually faithful, monogamous relationship in the context of marriage is the expected standard of human sexual behavior (5).

The Obama administration's intent was to end most abstinence-only education programs in favor of comprehensive sexual education, but Congress reinstated \$250 million of federal funding for abstinence-only education over a 5-year period. During the last 10 years, taxpayers have supported abstinence-only education programs for adolescents at a cost of more than a billion dollars (6).

Abstinence-only sex education has been extensively evaluated using such outcome measures as sexual debut, number of sexual partners, effectiveness of virginity pledges, acquisition of sexually transmitted diseases (STDs), and use of contraceptives at first sex. Current research suggests not only that abstinence-only education is ineffective, but also that parents overwhelmingly support comprehensive sex education (7).

Comprehensive sex education that includes abstinence, contraception, and STD prevention seems to optimize reproductive health outcomes (8–10). Abstinence only education can do harm: for example, studies of virginity pledges, a common component of several popular abstinence-only education programs, suggest that although pledgers are just as likely to have premarital sex as nonpledgers, they are less likely than nonpledgers to avail themselves of contraception or STD protection (11) A recent Cochrane review published through the Cochrane Database of Systematic Reviews

concluded that educational and contraceptive-promoting interventions reduce unintended pregnancy in adolescents (12).

Evidence strongly supports comprehensive sex education. In 2010 funds became available under the Patient Protection and Affordable Care Act (ACA) for scientifically sound programs that draw on curriculum-based sex education or youth development approaches to prevent teenage pregnancy. Despite mounting evidence of the benefits of comprehensive sex education, the young are less likely today than they were in 1995 or between 2006 and 2010 to receive instruction on contraception (13). Healthy People 2020 data show a decrease in the percentage of women and men younger than 18 given formal instruction about contraceptive methods. Compared with responses from the 2006 to 2010 period, responses from 2011 to 2013 showed a drop in reported formal birth control education for women from 70% to 60% and for men from 61% to 55% (13). This reduction is not surprising given the keen focus and massive funding dedicated to abstinence-only sex education over three decades. At coital debut, 79% of female teenagers and 84% of male teenagers used a contraceptive method. Less effective methods, such as condoms, remain the most common contraceptive choice in this age group (14).

Amid debates on the merits of abstinence-only-until-marriage education versus comprehensive sex education, oddly no federal requirements for the content of sexuality education exist. Some states have created requirements for sex education and human immunodeficiency virus (HIV) prevention but curricula vary widely between states (15). Whereas 24 states mandate sex education and 18 require information on contraception,

37 states mandate information. Eighteen states require information on contraception and 13 states require that the instruction be medically accurate.

Yet overall despite some state requirements, an analysis of NSFG data showed declines in receipt of formal sex education and disparities between rural and urban areas; adolescents living in nonmetropolitan areas were significantly less apt to obtain instruction in such topics as abstinence, birth control, and STD prevention (16).

Ironically, despite the inconsistency of sexuality education in the United States, over time some positive changes in teenage sexual activity have occurred (17,18). From 1995 to 2011 to 2013, fewer teenagers younger than age 15 had become sexually active. From 1982 to 2011 to 2013, more teenagers used contraception at first sex (48% vs 79%). Reductions in formal comprehensive sex education have occurred over the same time period that has seen a drop in teenage birth rates.

Teenagers do not seem to receive additional information from other sources, such as parents or friends; as for social media, its effect is unknown. Although teenage pregnancy rates are lower, widespread adoption of comprehensive sex education has the potential to reduce these rates further. Additionally, a host of professional organizations, including the Society for Adolescent Medicine, the American College of Obstetrics & Gynecology, and the American Pediatrics Association strongly support comprehensive sexuality education, including refusal skills, abstinence, and contraception. The American Academy of Pediatrics (AAP) offered testimony to the House Committee on Oversight and Government reform on behalf of its membership and that of the American Society of Adolescent Medicine, urging funds for comprehensive sex education (19).

The CDC Healthy People 2020 goals incorporate sexuality education goals,

including increasing the percentage of females younger than 18 who receive formal instruction in birth control to 78%, and the percentage of males younger than 18 to 67%. These targets are in alignment with the evidence of the near universality of premarital sex, and of sexual debut by more than half of all women and men by age 18 (17,18). Although age at sexual debut has decreased, common sense dictates that the provision of information for most teenagers who do have sex is bound to have a positive impact on unintended pregnancy and on STD acquisition.

INFLUENCE OF MEDIA ON UNINTENDED PREGNANCY

A disconnect remains between the halting steps toward comprehensive sexuality education and current content of many forms of media, saturated with sex. Although the United States has not embraced comprehensive sexuality education for youth, it has thoroughly adopted the use of sex for advertising a wide range of products. Sexual content also figures large in a range of television shows, from sit-coms to reality television and little of that content conveys messages about responsible sex, including monogamy or safe sex (20). This schizophrenic approach—to deny in the classroom what is sold in the marketplace—seems distinctly American. We refuse to engage with young people in serious conversations about sex, conversations that could help prevent unwanted pregnancy and STDs and help youth better understand how sexuality may contribute to well-being. Pervasive American morality seems at odds with accepting sexuality as a normal part of human behavior. This leaves many individuals, but particularly youth, confused, with a double standard that creates obstacles to the avoidance of unintended pregnancy.

Americans spend considerable “screen time” between television, mobile devices, and computer use. In 2013 a comprehensive survey studied teenage media use. Two media activities dominated: television and music. The survey found that teenagers use an average of 9 hours of media every day. Those from low-income families use media for considerably more time than teenagers from higher-income families (21). For “screen” media, lower-income teenagers averaged 8.07 hours a day, whereas higher-income teenagers averaged 5.42 hours.

The potential impact of sexual content on television is important, given the great amount of time Americans spend watching television. In 1998, a total of 56% of television shows contained sexual content, with an average of 3.2 scenes per hour. By 2005, the percentage of shows that included sexual content increased to 70%, with an average of five scenes per hour (20). Although the Kaiser Family Foundation no longer studies the sexual content of television shows, the Parents Television Council, continues to watchdog content. The Parents Television Council issued a report finding that sexual references in shows had increased by 22% (22).

Evidence is conflicting regarding the impact of television’s sexual content on the sexual behavior of teenagers, although numerous studies attest to the influence on teenagers’ attitudes toward sex and on their values and beliefs. A recent study of youth aged 12 to 17 demonstrated a higher likelihood of teenage pregnancy in the 3 years following frequent exposure to television’s sexual content including a mix of dramas, comedy, reality, and animated programming (23). Teenage pregnancy in the high-exposure groups was twice the rate of the low-exposure group, even after adjusting for confounders. Most evidence seems to support an association between

more frequent and more sexually explicit viewing as a risk factor for unsafe sexual behavior. These associations led the AAP to publish a strongly worded policy statement directed at pediatricians and the entertainment/broadcast industry (24). Among the recommendations were these: counseling parents to be aware of and limit teenagers' screen time, encouraging the entertainment industry to produce more programming with responsible sexual content, and urging the broadcast industry to expand airtime for advertising of contraceptives.

Media can also have a positive impact. Several television programs have incorporated positive health-related messaging. *Gray's Anatomy* and *ER* dramatized story lines that educated the public about human papilloma virus, emergency contraception, and HIV. In an innovative trial involving social media, messaging was used to increase condom use among at-risk youth. The results showed some evidence of effectiveness (25). As urged by the AAP, expansion of contraception advertising could have a positive effect on reducing unintended pregnancy. Lack of or highly restricted advertising for contraceptives has been the norm. In the United Kingdom, the AIDS epidemic prompted networks to allow condom advertisements in primetime, rather than confine them to an after 9 PM time slot (26).

Overall, however, the combination of explicit sexual content in media with limited "responsible" sexuality content or contraceptive advertising constitutes a barrier to reducing unintended pregnancy. Disparities in the consumption of media by lower income youth may result in additional negative consequences.

CULTURE AND FAMILY PLANNING

Cultural norms may result in unconscious bias that perpetuates negative stereotypes of minority women. In 2011, the birth rate for non-Hispanic white teenagers (21.7 per 1000) was less than half that among non-Hispanic black teenagers and Hispanic teenagers (at 47.2 and 49.6 per 1000, respectively) (Fig. 2) (27). This disparity mirrors broader disproportionately adverse health care outcomes occurring within communities of color. Many well-intentioned reproductive health interventions have therefore “targeted” specific communities for an intensive focus on reducing unplanned pregnancy, a practice that can lead to unintended consequences.

Standard expectations for “acceptable” parenting, including age at first birth, family size, and intention to become pregnant, are set by the dominant culture (28). Members of the dominant culture, high income non-Hispanic whites, are overrepresented in medicine and largely responsible for the reproductive health counseling of young women. Lack of appreciation of the power differential between patient and provider, and cultural biases can unintentionally result in reproductive coercion toward use of contraception and use of specific methods and moral condemnation for reproductive choices and outcomes (29–31). Although access to contraception may decrease pregnancy, birth, and abortion rates, social determinants may be much more powerful mediators of high birth rates in communities of color. These social determinants involve several inequities experienced daily by members of the non-dominant culture (4). Health care providers must focus on providing knowledge and access to full-spectrum contraceptive options so that women and men are able to make autonomous, well informed choices grounded in a shared decision-making model.

ACCESS TO CARE: THE IMPACT OF THE AFFORDABLE CARE ACT

Almost every American woman will use a method of contraception at some point in her life (99%). The average American woman spends 30 years preventing pregnancy (32). Numerous publications appropriately emphasize the cost savings of contraceptive insurance coverage. But even when contraception is “covered,” lack of adequate insurance coverage, such as high out-of-pocket costs in the form of copays and deductibles, is a barrier to the affordability of desired methods.

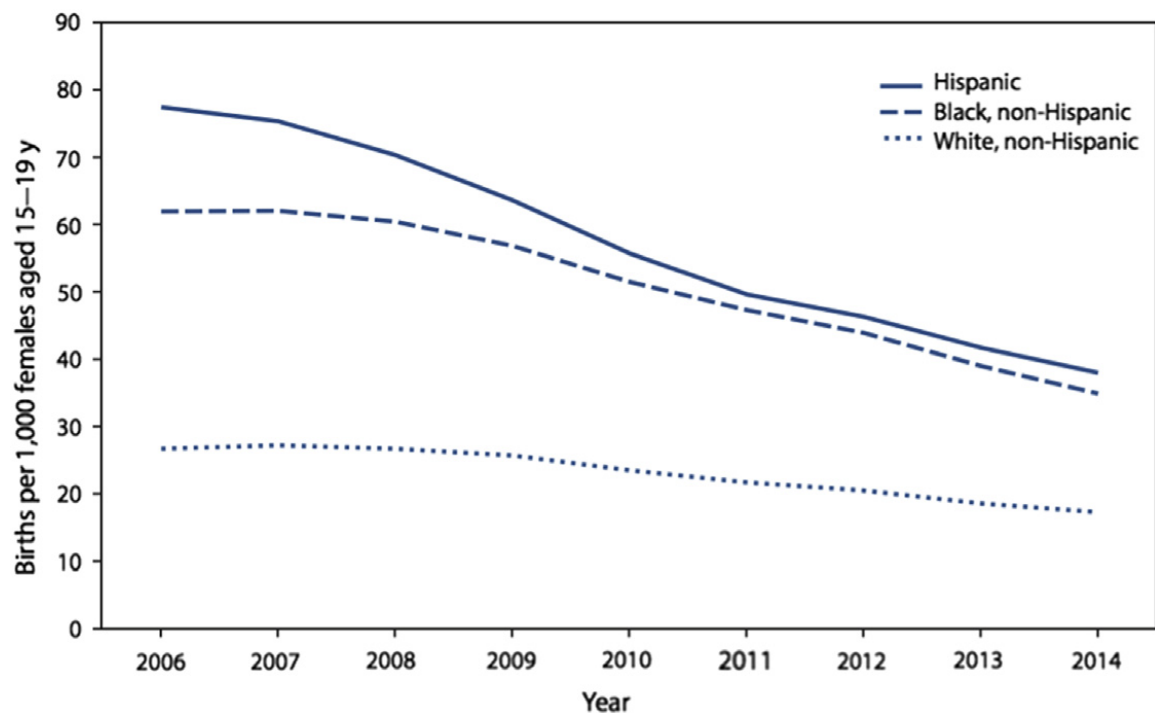


Fig. 2. Birth rates for females aged 15 to 19 years during 2006 to 2014. (From Romero L, Pazol K, Warner L, et al. Reduced disparities in birth rates among teens aged 15–19 years— United States, 2006–2007 and 2013–2014. *Morb Mortal Wkly Rep* 2016;65:411. Available at: <http://www.cdc.gov/mmwr/volumes/65/wr/mm6516a1.htm?version=metric1at1null&module=metric-Links&pgtype=article&contentId5&mediaId5&referrer5&priority5true&action5click&contentCollection5meter-links-click>. Accessed August 8, 2016.)

The most highly effective reversible methods, intrauterine devices (IUDs) and implants, have high up-front costs despite their long-term cost-effectiveness. In the 2012 NSFG, 11.6% of women reported use of an IUD or implant (33), a major increase from the prior reporting period, but considerably less than the uptake in many studies of

LARC. In the Contraceptive CHOICE study, a large cohort trial conducted in St. Louis, Missouri, 75% of women chose an IUD or implant for contraception when women were offered all methods without financial barriers (33).

To address the national health care delivery crisis, in 2010 President Obama signed the ACA into law. Based on recommendations from the Institute of Medicine (34), the Health Resources and Services Administration mandated coverage of “Food and Drug Administration approved contraceptive methods, sterilization procedures, and patient education and counseling for women with reproductive capacity” with at least one form of each type of contraceptive covered without cost sharing (35)

The impact of the ACA was swift: the proportion of reproductive-aged women who were uninsured fell by 40%. Many women for the first time were able to afford their desired contraceptive method. The number of women who filled prescriptions for birth control pills with no copay exploded, from 1.2 million in 2012 to 5.1 million in 2013 (36). Nationwide claims database research reveals that from 2011 to 2013, the mean copay per contraceptive claim decreased 73%, from \$15 to \$4. Additionally, the number of commercially insured women with \$0 out-of-pocket cost for any contraceptive increased from 10.1% in 2011 to 69.6% in 2013 (37). In 2014, a total of 87% of insured women were able to obtain an IUD without out-of-pocket costs (Fig. 3 data from the

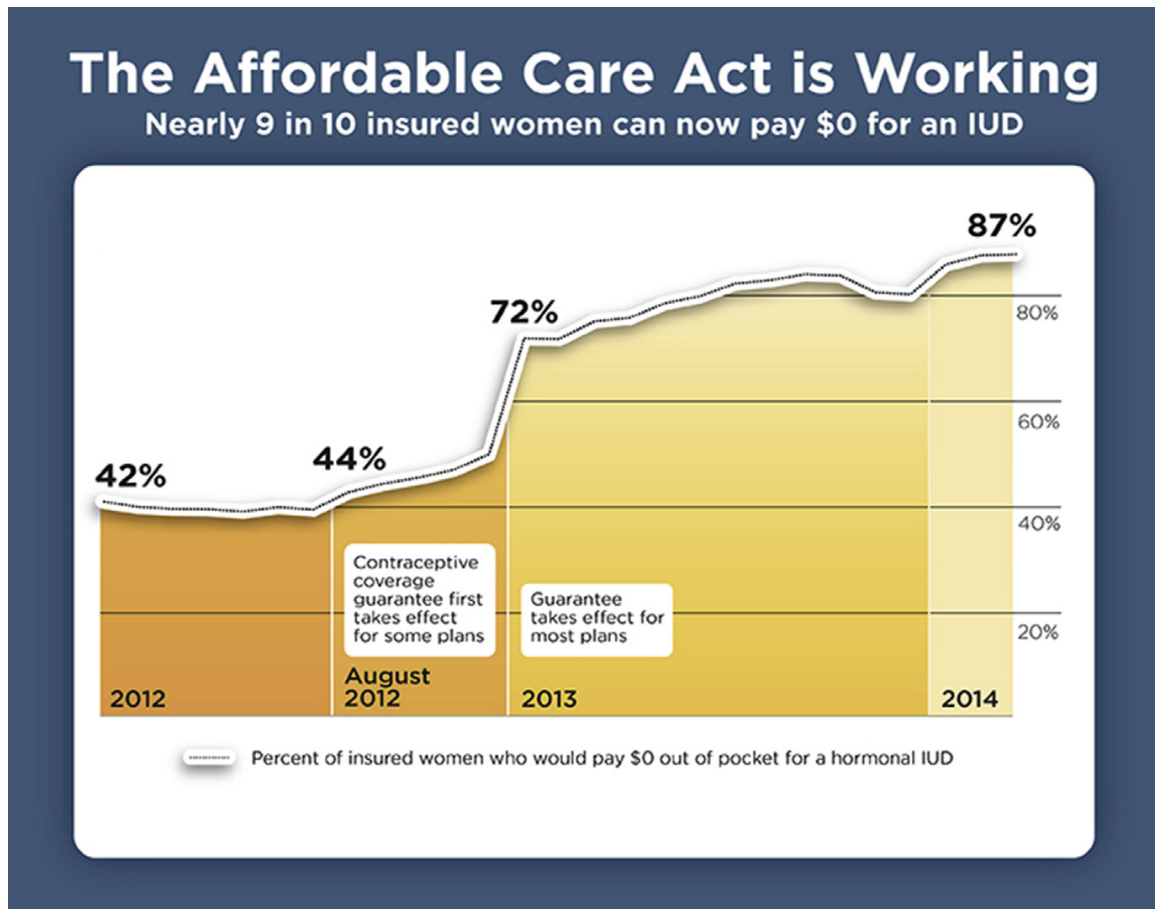


Fig. 3. The Affordable Care Act contraceptive mandate has made contraception more financially attainable for insured women. (From Guttmacher Institute. *The Affordable Care Act is working*. Infographic. New York: Guttmacher Institute; 2016. Available at: <https://www.guttmacher.org/infographic/2015/affordable-care-act-working>; with permission.)

Guttmacher Institute) (32). By reducing out-of-pocket costs for insured women, the ACA contraceptive mandate has made contraception more financially attainable.

ANTICONTRACEPTIVE POLITICS

Since its inception, the contraception mandate has been mired in religiously motivated activism and anticontraception politics. A vocal minority holds that contraception promotes societal problems, such as promiscuity, an antichild attitude, and the undermining of traditional male-female relationships (38). Until recently, most experts agreed that improved contraceptive use was a major component in efforts to

decrease abortion. A more radical view is that the provider of contraception violates morality. The Catholic doctrine that “every “marital sexual act must be open to the possibility of the transmission of life,” (39) is not supported by the reality that almost all Catholic women have used contraception during their lives (40). Deplorably, scientific misinformation about the mechanism of action of many contraceptives has led antiabortion activists to oppose several contraceptives. Increasingly, contraception and abortion politics are polarized, partisan topics (41).

In February 2012, the Republican-led House Oversight and Government Reform Committee organized a hostile review of the ACA contraceptive mandate, claiming it to be an “assault against their freedom of conscience.” (42) Specifically, House members asserted that the contraceptive mandate violated the religious freedoms of certain employers whose faith teaches the immorality of contraception. The panel was exclusively composed of male theologians and clergy hearing testimonials from adherents of religious organizations and institutions.

Democratic members of the Committee requested the addition of Georgetown law student, Sandra Fluke, to the list of witnesses. Ms. Fluke had firsthand experience of the difficulties in seeking reproductive health care at a religious university. The Committee Chairman, Darrell Issa, denied the request on technical grounds, adding that Ms. Fluke lacked sufficient experience. Chairwoman Nancy Pelosi then convened a meeting of the Democratic Steering and Policy Committee and offered Sandra Fluke the opportunity to testify. Her testimony outlined the personal experiences of women enrolled at Georgetown University who were unable to obtain full spectrum health care because of the faith-based limitations of their insurance coverage.

Ms. Fluke and her testimonial were criticized by political commentator Rush Limbaugh in his radio talk show. He called Fluke a “slut” and a “prostitute” stating that “she’s having so much sex she can’t afford her own birth control pills.” Although mainstream media condemned his misogyny, “slut shaming” remains a tactic used by conservative thought leaders to shut down discussion of the contraceptive mandate. The acrimony of the conservative response to Ms. Fluke reflects the increasingly controversial nature of contraception.

In 2012, the Green family, Evangelical Christian owners of the arts and crafts business, Hobby Lobby, dropped coverage of two types of contraceptives (IUDs and emergency contraception pills). They brought suit against the government asserting that the mandate interfered with their religious freedom, citing the Religious Freedom Restoration Act. The Green family defined IUDs and emergency contraception pills as abortifacients, counter to the medical definition of abortifacients, which act after implantation. The US Supreme Court accepted the case in *Burwell v. Hobby Lobby*; in a landmark decision, the Court ruled that closely held for-profit corporations could file for a religious exemption to the contraceptive mandate. As Justice Ruth Bader Ginsburg pointed out in her dissent, “the court, I fear, has ventured into a minefield.” The implications of this decision are broad insofar as they conflate a critical public health prevention strategy and the interests of women’s health with a violation of religious freedom.

HOSPITAL MERGERS

A systems barrier to reducing unintended pregnancy is the negative impact on

reproductive health services that occurs when nonsectarian hospitals merge with religious, particularly Catholic, hospitals. In the 10 years from 2001 to 2011, the number of Catholic hospitals increased 16%, more than any other type of nonprofit hospital (Fig. 4). Ten of the largest 25 health systems in America are Catholic (43). In 2016, one in every six acute care hospital beds is in a Catholic owned or Catholic affiliated hospital (44).

These mergers mean that more and more Americans are being treated in Catholic facilities, which operate under the explicit requirements embodied in the Ethical and Religious Directives (ERDs) for Catholic Health Care Services (45). Among other services, these directives explicitly oppose abortion, family planning, sterilization of men and women, emergency contraception, and HIV counseling that includes information about condom use. Mergers between nonsectarian and Catholic hospitals often result in the elimination or severe restriction of reproductive health services. In some states, a Catholic owned or affiliated hospital may be the only local hospital.

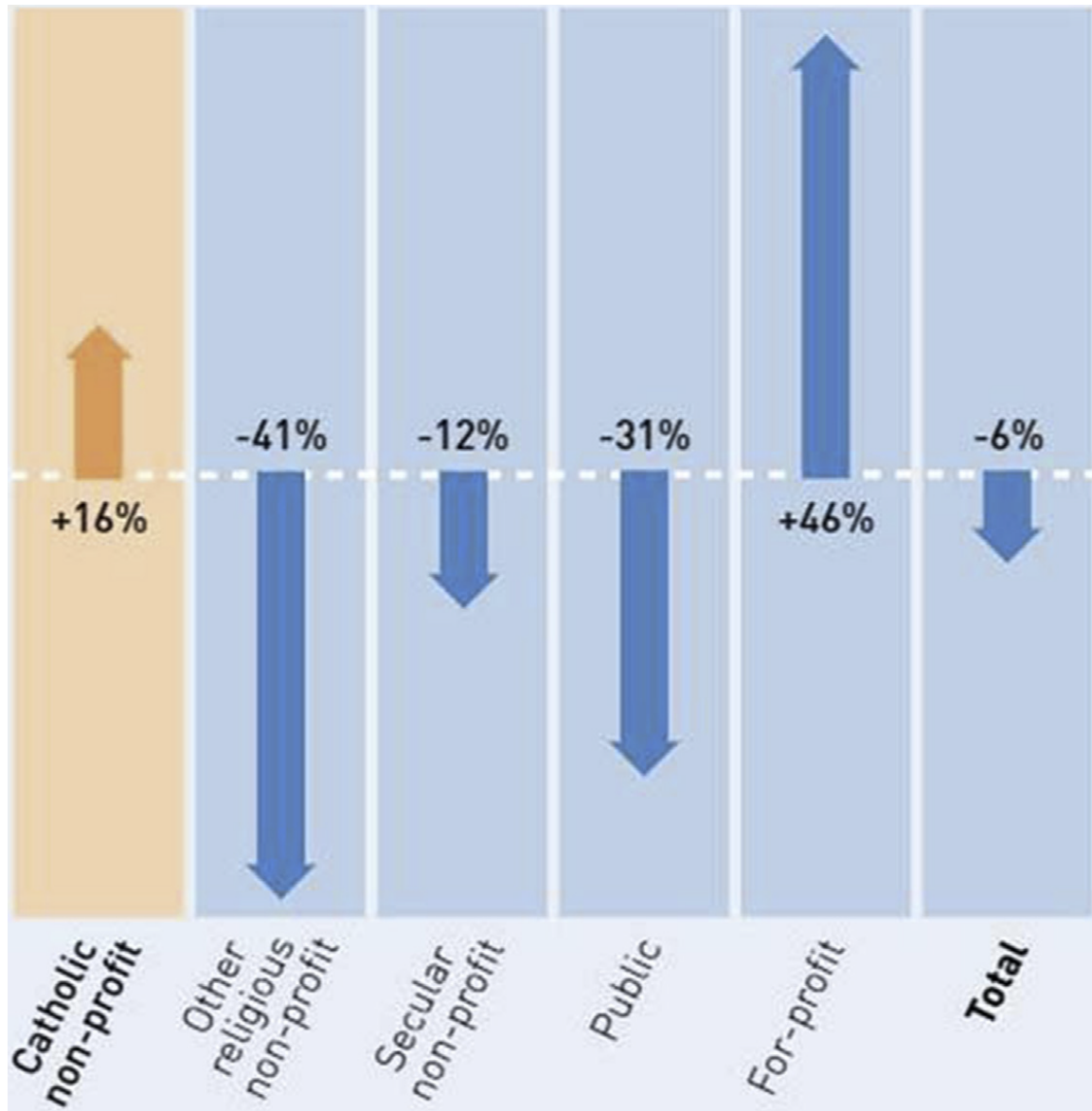


Fig. 4. Percentage change in number of acute-care hospitals by hospital type from 2001 to 2011. (From Uttley L, Reynertson S, Kenny L, et al. Miscarriage of medicine: the growth of Catholic hospitals and the threat to reproductive health care. American Civil Liberties Union and the MergerWatch Project. 2013. Available at: <https://www.aclu.org/report/miscarriagemedicine>. Accessed August 9, 2016; with permission. Courtesy of MergerWatch and the ACLU. Artist: Brucie Rosch.)

The impact of the ERD restrictions on reproductive health care should not be ignored. Public activism is a successful strategy. The National Women's Law Center developed the Health Care Provider Merger Project, which uses legal tools to focus

attention on the ERD restrictions at the local level (46). The American Civil Liberties Union recommends national activism to press for investigation into Catholic hospitals for violation of Centers for Medicare and Medicaid Services requirements that all hospitals provide emergency health care regardless of religious affiliation. On an individual level, the American Civil Liberties Union encourages patients to learn whether or not their local hospitals are Catholic run or affiliated and which services are offered (47).

WHO IS MOST AFFECTED?

Despite the advances in access because of the ACA, certain groups remain at a disadvantage. Objections to ACA coverage of contraception disproportionately affect women already at risk for gaps in coverage including minors, women of color, and women residing in Medicaid nonexpansion states (48).

Despite professional societies' recommendations to routinely offer highly effective methods, such as IUDs and implants, to adolescents and young women as first-line contraception (49), uptake remains low. Some postulate that confidentiality may drive nonuse because some states require parental notification of contraceptive services. A 2003 to 2004 survey finds one in five adolescents stating that if faced with mandatory parental notification laws, they would use not contraception at all or rely on withdrawal (50). Where parental notification is not mandated, teenagers enrolled in their parents' health plans may nevertheless fear loss of confidentiality via explanation of benefits or copays.

Latina women are also less apt to have adequate coverage for reproductive health

services despite the ACA. Compared with white women, Latinas have twice the odds of being uninsured and this discrepancy is even more stark among immigrant Latina women (Fig. 5) (51) These statistics indicate that institutional and policy barriers are major obstacles to contraception for women of color.

As of July 2016, a total of 19 states have chosen to opt out of Medicaid expansion under the ACA including Alabama, Florida, Georgia, Idaho, Kansas, Maine, Mississippi, Missouri, Nebraska, North Carolina, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Wisconsin, and Wyoming (Fig. 6) (52). In these states, women had twice the odds of being uninsured after implementation of the ACA.

FACILITATORS

Although many barriers impede access to family planning services, the last decade has also seen a resurgence of facilitators promoting women's ability to successfully plan their families. Providers have become more comfortable with an expanded candidate profile and with the techniques for placement of IUDs and implants. The American College of Obstetricians and Gynecologists recommends an expanded profile of candidates thought appropriate for IUDs, including adolescents and nulliparous women (53). Using a model of shared, nondirective decision making, providers are encouraged to review with patients their reproductive health goals and the range of methods for achieving them.

The American College of Obstetricians and Gynecologists supports other access facilitators, such as same-day initiation of methods, no unnecessary additional medical appointments, and no required pelvic examinations or STD testing before receipt of a

method (54). Medically unnecessary steps create a heavier burden for women seeking

Immigrant women need health coverage, not legal barriers.

The 6.5 million U.S. women of reproductive age who are not citizens are much less likely to be insured...

...especially those who live in poverty and are often barred from Medicaid.

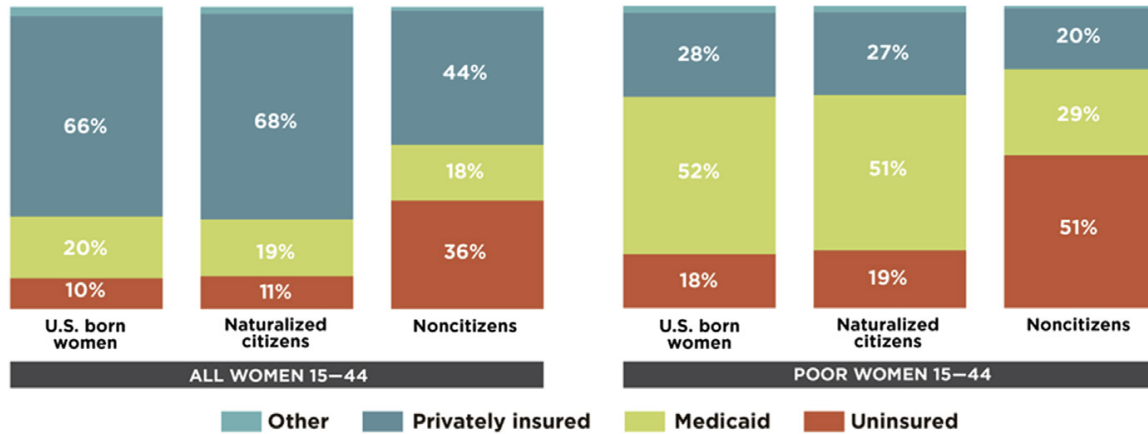


Fig. 5. Latina women are less apt to have adequate coverage for reproductive health services despite the ACA. Statistics indicate that institutional and policy barriers are major obstacles to contraception for women of color. Notes: Poor women are those in families with incomes under the federal poverty level (\$20,090 for a family of three in 2015). Data include some information on undocumented immigrants, although that information is generally acknowledged to be a considerable undercount of that population group. (From Guttmacher Institute. Immigrant women need health coverage, not legal barriers. Infographic. New York: Guttmacher Institute; 2016. Available at: <https://www.guttmacher.org/infographic/2016/immigrant-women-need-health-coverage-not-legal-barriers>; with permission; and Special tabulations of data from the 2016 American Community Survey (data are for 2015).)

Current Status of State Medicaid Expansion Decisions

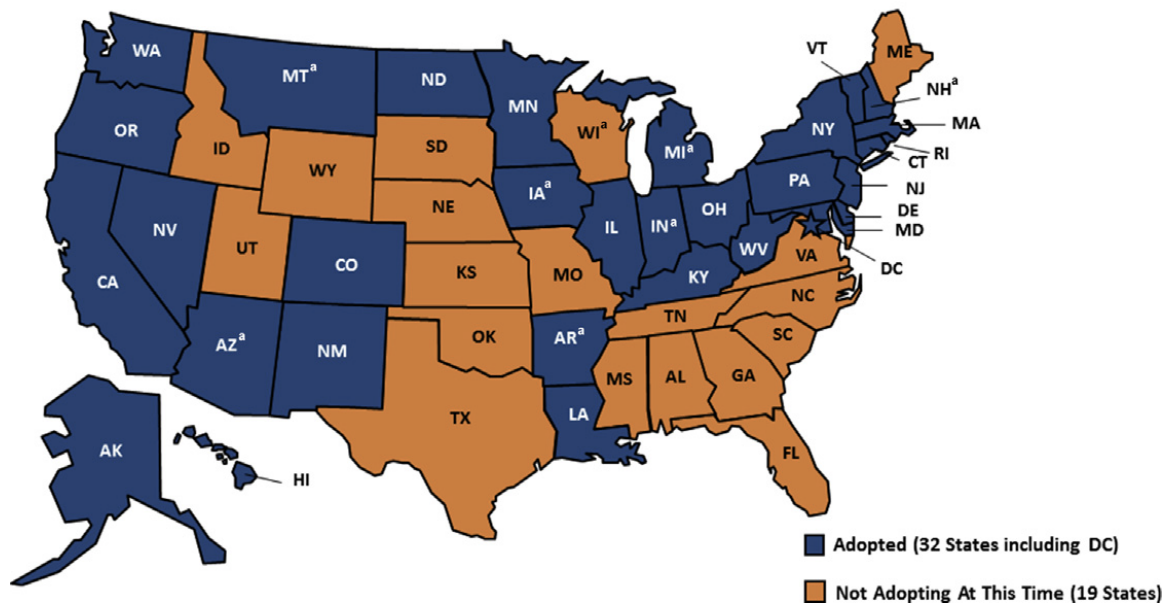


Fig. 6. As of July 2016, 19 states have chosen to opt out of Medicaid expansion under the ACA. Note: Current status for each state is based on KCMU tracking and analysis of state executive activity. a AR, AZ, IA, IN, MI, MT, and NH have approved Section 1115 waivers. WI covers adults up to 100% FPL in Medicaid, but did not adopt the ACA expansion. FPL, federal poverty level; KCMU; Kaiser Family Foundation's Commission on Medicaid and the Uninsured. (From Status of state action on the Medicaid expansion decision. The Henry J. Kaiser Family Foundation. Available at: <http://kff.org/health-reform/slide/current-status-of-the-medicaid-expansion-decision/>. Accessed August 9, 2016.)

contraception. Another principal facilitator is over-the-counter status for oral contraceptive pills (55). The greatest risk of oral contraceptives is venous thromboembolism; the argument for over-the-counter status is the rarity of the outcome (3–10.22 per 10,000 women years) compared with the considerably higher risks of pregnancy. Some states, such as California and Oregon as well as Washington and New Mexico now, have passed legislation allowing pharmacists to prescribe oral contraceptives (56). Immediate postpartum insertion of highly effective LARC methods is also gaining in popularity. The postpartum window is an ideal time for contraception because the patient is known not to be pregnant and she has ease of access to medical professionals (57,58). In several states, Medicaid has allowed the uncoupling of the global delivery fee from the LARC device and insertion, permitting hospitals to offer this service.

SUMMARY

In 2015, Latin America saw the spread of the mosquito-borne Zika virus. This disease, although typically asymptomatic, is known for the microcephalic babies born to women infected during pregnancy. In the summer of 2016, for the first time, the CDC issued a travel warning to a local city, Miami, Florida, because of a cluster of new cases (59). The spread of the virus has forced the discussion of reproductive health care in America and of the real-life impact that restrictive family planning and abortion policies

create. Although many health experts have indicated that women exposed to the virus should not get pregnant for at least 8 weeks following infection, few policies have translated into actionable plans to meet these reproductive health goals. Systems approaches that focus on education and access to care are critical (60,61). The ability to prevent the devastating consequences of infection depends on making family planning services available to all. Availability is ineffective without education and education alone is insufficient without policy change.

Contraception has become a new political battle ground across the United States and in the nation's capital. American women and families are the victims of this battle; politicization of abortion and contraception harms Americans seeking access to basic health care. Promotion of contraception should occur at every level, from early and comprehensive sexual education to responsible media. Recommendations of religious leaders and politicians should not supersede those made by leagues of health professionals.

Accomplishing health equity starts by recognition that disparities exist. Disparities in reproductive health outcomes based on socioeconomic status and race/ethnicity are compounded by the controversial nature of reproductive health care services. Society's reluctance to accept the reality and impact of reproductive health care needs widens the equity gap. In health care, it is time that Americans turn the spotlight on reproduction. So long as reproductive health care is deemed exceptional or outside of the purview of medicine, Americans will continue to suffer the consequences.

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CHAPTER 2

Efficacy of Extending Contraceptive Implant Duration: A Systematic Review

Introduction

Progestin-only implants are highly effective contraceptive methods with less than 1% of women experiencing an unintended pregnancy in the first year of use (1)(2)(3). Women of all ages are interested in the contraceptive implant because of its long duration of action, reversibility and efficacy (4)(5)(6)(Kennedy C., *Values and preferences in contraceptive decision making: a systematic review*, unpublished data submitted for publication, 2017). Implants can also be highly cost effective (7)(8). Contraindications to implants are uncommon due to the lack of an estrogen component (9). Implants exhibit high continuation rates and represent an increasing proportion of the contraceptive method mix.

Implants have three probable mechanisms of action: suppression of ovulation, thickening of cervical mucus, and endometrial atrophy (3). Two subdermal progestin implants are currently available globally: etonogestrel (ENG)-releasing (including the Implanon® and Nexplanon®) and levonorgestrel (LNG)-releasing (including the Sino-Implant II and Jadelle®) devices (10)(11). The description for each of these devices is included in Table 1.

Table 1: Description of Devices

Device Brand Names	Manufacturer	Progestin	Rod	Recommended Duration of Use (years)
Nexplanon, Implanon	Merck	68 mg ENG	1	3
Sino-Implant (II), Levoplant, Femplant, Trust, Zarin	Shanghai Dahua Pharmaceuticals Co., Ltd	75 mg LNG	2	4
Jadelle	Bayer	75 mg LNG	2	5

Despite benefits, barriers to obtaining a progestin-only implant are reported among women who desire them, including access to trained professionals for placement and removal and high up front device costs. Efforts have been made to take advantage of convenient opportunities for placement, such as immediately post pregnancy (12). Extending the duration beyond the currently approved length of use, if shown to be efficacious, could offer another means to enhance accessibility by maximizing the lifetime of the implant.

The purpose of this systematic review was to examine current evidence to answer the question “Can the use of contraceptive implants be extended beyond currently approved durations without compromising contraceptive efficacy?”

Sources

We searched published studies among PubMed and EMBASE, as well as ongoing clinical trials registered on CT.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). To locate articles within

PubMed and EMBASE, we used the following search terms for devices, developed together with a Health Science Librarian: “levonorgestrel”, “norplant”, “Jadelle®”, “etonogestrel”, “Implanon®”, “Nexplanon®” and “sino implant” as well as search terms for pregnancy outcomes (to assess contraceptive failure) and study designs including clinical trials or cohort studies. This resulted in the following search strategy for PubMed:

"Pregnant Women"[Mesh] OR "Pregnancy"[Mesh] OR "Pregnancy Complications"[Mesh] OR "Maternal Health Services"[Mesh] OR "Mothers"[Mesh] OR "Maternal Death"[Mesh] OR "Maternal-Fetal Relations"[Mesh] OR "Maternal Exposure"[Mesh] OR "Maternal Mortality"[Mesh] OR "Maternal Behavior"[Mesh] OR pregnan* [TIAB] OR Maternal*[TIAB] OR mother*[TIAB] OR child bearing [TIAB] OR perinatal [TIAB] OR Postnatal[TIAB] OR peri-natal [TIAB] OR post natal [TIAB] OR ante natal [TIAB] OR antenatal [TIAB] OR Postpartum [TIAB] OR puerperium [TIAB] OR post partum [TIAB] OR abortion* [TW] OR abortive [TW] OR "Abortion, Induced"[Mesh] AND (Animals [MH] NOT (Humans [MH] AND Animals[MH])) AND "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "clinical trials as topic"[mesh] OR "random allocation"[mesh] OR "double-blind method"[mesh] OR "single-blind method"[mesh] OR "clinical trial"[pt] OR "research design"[mesh:noexp] OR "comparative study"[pt] OR "evaluation studies"[pt] OR "follow-up studies"[mesh] OR "prospective studies"[mesh] OR "cross-over studies"[mesh]OR "clinical trial"[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw]) AND (mask*[tw] OR blind*[tw])) OR placebo*[tw] OR random*[tw] OR "control"[tw] OR "controls"[tw] OR prospecitv*[tw] OR volunteer*[tw] OR "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw]

OR "groups"[tw] OR "case control"[tw] OR "multivariable"[tw] AND
 ("levonorgestrel"[MeSH Terms] OR levonorgestrel[All Fields] OR norplant[All Fields]
 OR Jadelle®[All Fields] OR ("etonogestrel"[MeSH Terms] OR etonogestrel[All Fields]
 OR Implanon®[All Fields] OR Nexplanon®[All Fields] OR “sino implant” [TW]).

Articles published between January 1, 1996 and December 31, 2016 were included as FDA approval of the Jadelle® implant occurred in 1996 and all other devices were developed and released after this year. The search was not restricted with regards to country or language. To identify studies within ClinicalTrials.gov and ICTRP we used the following search terms: “levonorgestrel”, “norplant”, “Jadelle®”, “etonogestrel”, “Implanon®”, “Nexplanon®” and “sino implant” with participants limited to female children and adults.

Study Selection

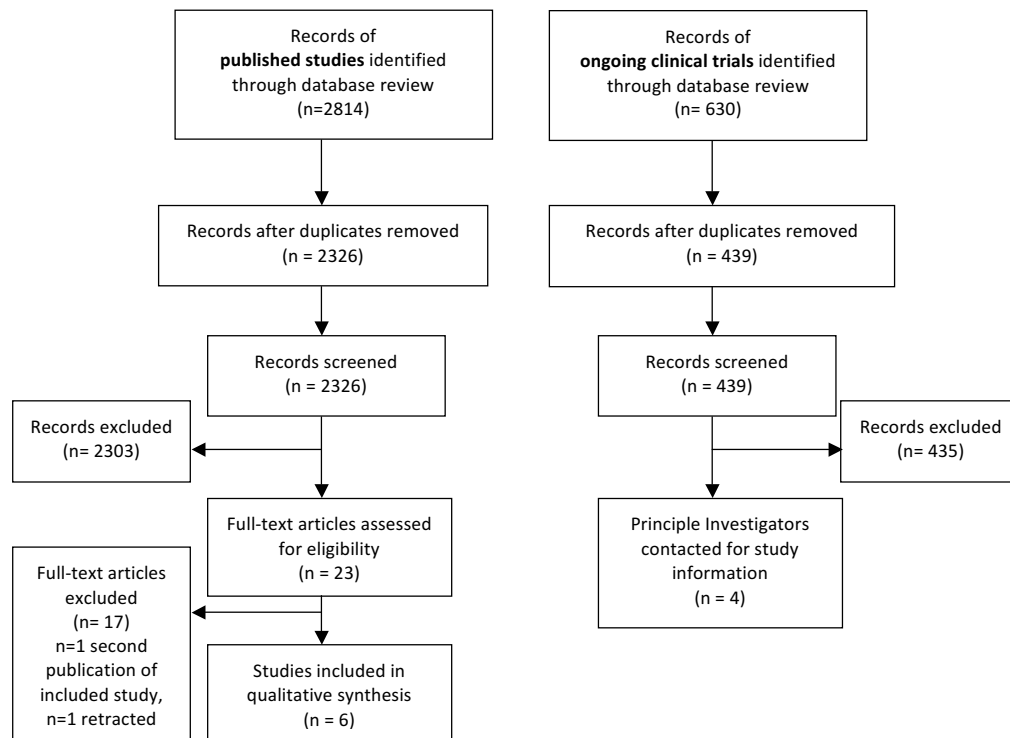
We included studies investigating the contraceptive effectiveness of extended use of levonorgestrel or etonogestrel implants beyond current approved durations. Studies evaluating the Norplant® were excluded as this device is no longer available. Additionally, studies evaluating contraceptive implants currently in pre-marketing trials were not included. Inclusion criteria included randomized clinical trials (RCTs), cohort or case-control studies with some measure of contraceptive efficacy of one of the four devices specified beyond the currently approved duration. Conference abstracts, posters or oral presentations were excluded. Studies included from ClinicalTrials.gov were eligible if they investigated one of the two etonogestrel implants, Implanon® or Nexplanon® as these implants are the only available in the United States. For ongoing

trials, we contacted corresponding authors to determine if any data could be included in this review.

The title and abstract from each article was evaluated by two independent reviewers to determine if the article met inclusion/exclusion criteria. The full text of the article was obtained if both reviewers judged a citation as potentially eligible; full text was screened for eligibility by both reviewers. No discrepancies were noted. Reasons for exclusion, including number of duplicates, were documented. Reviewers abstracted the following information from the remaining articles: study title, author and publication year, funding source, study design, population size, duration of extended use, type of implant and number of contraceptive failures. Using the United States Preventative Services Task Force guidelines, each article's study quality was rated as "poor", "fair" or "good" (13). This rating was based on methodological quality rating as assessed by reviewers along the following domains: assembly of appropriate comparison groups (including adequate description and execution of randomization in RCTs and assessment of potential confounders in cohort studies such as participant age), loss to follow up during the study and description of how pregnancy was assessed. Additionally, quality of data analysis and interpretation was assessed according to whether adjustments were performed for confounders and whether contraceptive efficacy was measured cumulatively or analysed separately among women beyond approved duration.

Results

Figure 1: CONSORT Diagram



We identified 439 ongoing clinical trials and, of these, selected 4 studies for further review based on published information on Clinical Trials.gov or ICTRP (Figure 1) (14). One study was complete, two active and not recruiting, and one was still recruiting (15)(16)(17)(18). We contacted primary investigators to obtain data where available. The single ongoing study published interim findings in January of 2017. In this prospective cohort study, 291 women using the ENG implant extended by two years: 223 (77%) used the method for greater than 12 additional months, and 102 (35%) for greater than 24 additional months. These women represented a diversity of BMIs with 23% overweight and 52% obese or morbidly obese. In total, study participants contributed 444 women-years of follow up with no documented pregnancies for a calculated five year Pearl Index of 0 per 100,000 women-years (18).

We identified 2,326 citations in the published literature and selected 23 articles for full-text screening after review of titles and abstract (Figure 1). Sixteen studies were excluded because they did not meet inclusion/exclusion criteria. One additional study was removed from the analysis as it represented a secondary publication and did not offer new data (19). Another article was removed as the data appeared to have been previously published and subsequently retracted in another journal due to erroneous data (20) (21). We included six studies in this systematic review resulting in a total of 1,357 women who self selected extended duration of their contraceptive implant (22)(23)(24)(25)(26) (27) (Table 2). Five studies evaluated the single-rod ENG implant (Implanon®), one evaluated the LNG implant, Jadelle®. No studies evaluated the Sino-Implant or Nexplanon® however, the Nexplanon® is simply a newer generation of the Implanon® with the same dose of ENG and pharmacokinetic properties. Four studies were sponsored by the manufacturer of the single-rod ENG implant. Only two studies separately evaluated contraceptive failure over the time frame of extended duration rather than cumulative use of the implant (23)(22).

The only RCT identified was part of a larger, multi-country study of healthy women desiring long-acting reversible contraception. Importantly, women were randomized to the type of contraception, single-rod ENG implant versus the 2-rod LNG implant, not the duration of use; women self-selected extended duration of the implant. Contraceptive failures were compared with a non-randomized control group of women who received the TCU380A Copper IUD (Pregna ®). A subset (N=390) of women randomized to the single-rod ENG implant consented to extended duration of use; 204 women completed five years of use (47% loss to follow up) with no reported pregnancies

for a calculated Kaplan-Meier cumulative pregnancy rate of 0.6 per 100 women-years (95% CI 0.2-1.8). Women randomized to the ENG versus the LNG implant noted similar side effects including irregular bleeding; users of the ENG implant exhibited higher rates of self-reported heavy menstrual bleeding. Removal time for the 1-rod ENG implant was additionally noted to be shorter in comparison to the 2-rod LNG implant (22).

The five remaining studies were prospective cohort in design. One study recruited women from a larger parent study of long-acting reversible contraception in St. Louis, USA. The parent study offered healthy, reproductive aged women desiring contraception access to contraceptive methods free of charge. Most participants elected use of an intrauterine system (IUS) or ENG implant (28). Those who consented to extending duration of their implants were followed and results of data collected during extension are reported here; this represents an interim analysis as recruitment and follow-up were ongoing at the time of publication. A total of 237 women consented to extended duration of their implant; 123 completed the fourth year and 34 completed the fifth year. Participants represented a broad range of body mass index (BMI); 42 (46%) were obese or morbidly obese. No pregnancies were reported during the follow up period. Additionally, 47 participants contributed to ENG serum analysis data at the fourth year, revealing a median ENG level of 170.0pg/ml (Range: 67.9, 470.5) with no differences across BMI groups (23).

All other studies evaluated contraceptive failures cumulatively over the entire use of the implant. A comparative study conducted in China examined women with extended use of the ENG implant and women using the 6-rod LNG implant. Among the 75 participants who received an ENG implant, 51 completed four years of use (32% loss to

follow up) with no reported pregnancies. Side effects included change in bleeding pattern, headache, breast tenderness and cramping. Additionally, women experienced a small increase in weight (3.5kg) and hemoglobin concentration, but no change in blood pressure (27).

Three of the studies were cohort studies, without a comparison group, evaluating women with extended use of the ENG implant for one year. No pregnancies were reported in any of these studies, although sample sizes were small for women completing the fourth year of implant use (N= 47 to 151) and loss to follow up was high. The most common reasons for discontinuations were desire to conceive or abnormal uterine bleeding; number of bleeding-spotting days was highest in the first few months of use. There were no changes in cervical cancer screening, hemoglobin levels or blood pressure. Small increases in weight occurred over study duration (1.1 to 2.9 kg). Insertion and removal times were short (less than five minutes) and return to fertility was rapid after implant removal (20)(25)(26).

A single study evaluated extended duration of the 2-rod LNG implant. A non-comparative prospective cohort study, it recruited 249 women to extended use of the LNG implant by one year. Only 58 women completed the additional year of use (77% loss to follow up); five women did not return for follow up for three or greater years. There were three diagnosed pregnancies in this study: one pregnancy was diagnosed prior to insertion of the implant and this participant was removed from analysis. A second pregnancy was diagnosed within the first month of implant use; the authors considered it likely a luteal phase pregnancy. The third pregnancy was diagnosed in the first year of extended duration (in the sixth year of use). The most common reason for early removal

of an implant was desire to conceive; implant removal times were shorter for the 2-rod LNG implant compared to historical times for removal of the 6-rod LNG implant (24).

Table 2: Summary of Included Studies

Author, Year	Title	Study design	Location	Study Size	Exposure	Duration	Pregnancy Outcomes	Women-Years Observed	Pearl Index	Strengths/Weaknesses	Quality
Alfandi B, Kover T, Geurts P et al 1999	<i>A phase II study with a single implant contraceptive containing 3-levonorgestrel (Implanon®): Efficacy and safety</i>	Non-randomized, non-comparative, prospective observational	Not discussed	N=200, N=124 entering 4th year and N=96 completing 4th year	1 rod ENG	up to 1 year extended use	Zero pregnancies	658.4	0 per 100 women-years	- Small population extending duration - Women self selected extended duration - No comparison group - Randomized clinical design, however randomized to contraceptive method NOT extended duration - Multiple study sites	Poor
Alli M, Akin A, Bahamonides L et al 2016	<i>Extended use up to 5 years of the etonogestrel-releasing subdermal contraceptive implant: comparison to levonorgestrel-releasing subdermal implant</i>	Multi-center, randomized clinical trial	Brazil, Chile, Dominican Republic, Thailand, Turkey, Zimbabwe	N= 390 with N=311 entering 5th year and N=204 completing 5th year	1 rod ENG	up to 2 years extended use	Zero pregnancies	204.5	0.6 per 100 women-years [95% CI: 0.2- 1.8]	- Small population extending duration - Women self selected extended duration - No comparison group - Assessed ancillary methods of contraception (barrier methods etc) - Assessed comorbidity that may affect fertility	Fair
Kirawat O, Pananyindee A, Koesawang S et al 1998	<i>A 4-year pilot study on the efficacy and safety of Implanon, a single-rod hormonal contraceptive implant, in healthy women in Thailand</i>	Non-randomized, non-comparative, prospective observational	Thailand	N=100 with N=47 completing 4th year	1 rod ENG	up to 1 year extended use	Zero pregnancies	296.1	Not calculated	- No comparison group extended duration - Women self selected extended duration - Assessed ancillary methods of contraception (barrier methods etc) - Assessed comorbidity that may affect fertility	Poor
McNicholas C, Maddipati R, Zhuo Q et al 2015	<i>Use of the etonogestrel implant and levonorgestrel intrauterine device beyond the U.S. Food and Drug Administration-approved duration</i>	Non-randomized, comparative, prospective observational	US	N=237 with N=123 completing 4th year and N=34 completing 5th year	1 rod ENG	up to 2 years extended use	Zero pregnancies	229.4	0 per 100 women-years (one-sided 97.5% CI: 0, 1.61)	- Small population extending duration - Women self selected extended duration - No comparison group - Age at enrollment was <35 years old - Homogenous population extended duration - Women self selected extended duration - Women self selected extended duration	Poor
Wan L, Silber A, Lam L 2003	<i>The levonorgestrel two-rod implant for long-acting contraception: 10 years of clinical experience</i>	Multi-center, non-randomized, non-comparative, prospective observational	US	N=249 with N=58 continued into 6th and 7th years, N=5 did not return for removal until 8th and 9th year	2 rod LNG	up to 1 year extended use	Zero pregnancies	823	0.24 per 100 women-years	- Small population extending duration - Women self selected extended duration - No comparison group - Age at enrollment was <35 years old - Homogenous population extended duration - Women self selected extended duration - Women self selected extended duration	Poor
Zheng S, Zheng H, Qian S et al 1999	<i>A long-term study of the efficacy and acceptability of a single-rod hormonal contraceptive implant (Implanon) in healthy women in China</i>	Non-comparative, multicenter prospective observational	China	N=200 with N=157 entering 4th year and N=151 completing 4th year	1 rod ENG	up to 1 year extended use	Zero pregnancies	644.6	Not calculated	- Small population extending duration - Women self selected extended duration - No comparison group	Poor
Yao X and Du M 2003	<i>A randomized study comparing the efficacy and bleeding pattern of Implanon and Nonplan hormonal contraceptive implant</i>	Non-randomized, comparative, prospective observational	Not discussed	N=75 with N=51 completing the 4th year	1 rod ENG	up to 1 year extended use	Zero pregnancies	Not reported	Not reported	- Small population extending duration - Women self selected extended duration - No comparison group	Poor

Discussion

Six published studies enrolling a total of 1,357 women and assessing extended duration of a progestin contraceptive implant were identified, with only three reported pregnancies, all among women using the LNG implant. Cumulative contraceptive failure rates in these studies are far below the typical use failure rate of many popular user-dependent methods such as oral contraceptive pills (1).

Pharmacokinetic studies of serum ENG are reassuring with regard to extended duration of the ENG contraceptive implant. Prior work indicates that ovulation is suppressed at serum ENG levels greater than 90 pg/mL (29). Women may exhibit wide ranges of ENG, with some values below 90 pg/ml. Median ENG levels at the end of three years of use of the implant are beyond this value at 207.7 pg/mL (range 63.8-802.6 pg/mL). Median serum ENG levels remain high at 166.1 pg/mL (range 25-470.5 pg/mL) at four years of use and 153.0 pg/mL (range 72.1-538.8pg/mL) at five years of use (18). Furthermore, McNicholas failed to show a difference in median serum ENG levels across BMI groups, including obese women, at the end of the fifth year of implant use (18). A similar pharmacokinetic study evaluated the minimum necessary LNG serum concentration to prevent pregnancy. In this study, pregnancies were identified in five women using the Jadelle® 2-rod LNG implant beyond five years. In all women, the serum LNG levels fell to or below 180 pg/mL (30).

Importantly, the pharmacokinetic data on ENG and LNG has revealed that serum concentrations between participants and even within the same participant over multiple collections vary widely. It remains unclear what ENG level is needed to provide effective

contraception, given the implant's other mechanisms of action including cervical mucus thickening and endometrial atrophy.

This systematic review has several limitations; results must be interpreted with caution. All six studies are of poor to fair quality. Only one study randomized participants to contraceptive method; no studies randomized participants to extended duration. Participants who elected to extend duration may differ widely from those who chose not to; important confounders such as risk of pregnancy were not addressed, raising concerns of selection bias. Two studies separately analyzed contraceptive failures among women within the extended duration; the other four analyzed cumulative pregnancy rates over total duration of implant use. Sample sizes were relatively small (N=75 to 390) and loss to follow up was high (25-86%). This could result in a falsely lowered pregnancy risk, as pregnancies were diagnosed based on clinical concern at follow up appointments. Four of the seven studies were industry sponsored. Few studies reported use of ancillary contraception such as barrier methods as an exclusion criteria or reported additional analysis to account for increasing participant age and possible decreased fecundity over the study period. No studies were identified to inform guidance about the Sino-Implant II or Nexplanon®. Inclusion and exclusion criteria for all studies defined participants as medically healthy, limiting generalizability.

If found to be efficacious, the ability to extend duration of contraceptive implants would serve to increase cost effectiveness of the device while decreasing barriers on women by reducing the number of visits needed for implant removal and reinsertion. While the findings of these studies report reassuring data for women considering extended duration of implant use, more quality research is needed to confirm findings,

guide clinical decision-making, and provide generalizable information to health programs in different settings. Future research should attempt to address high participant attrition and either engage in randomization of extended duration or critically evaluate potential confounders in continuation. Future studies also need to address a variety of BMI categories before conclusions can be made about overweight or obese women. Additionally, more pharmacokinetic research is needed on ENG and LNG serum levels as they relate to the outcome of interest: contraceptive failure.

Based on the current evidence, providers may consider the reassuring but limited data on extension of the ETG implant by one year. However more high quality research is needed before making generalized statements in support of extended duration. When counselling individual women, providers must consider the context in which a woman lives (e.g., access to health care, socio-economic situation), her medical history including obesity and potential drug-drug interactions and the risk of an unintended pregnancy and what it may mean to the woman. Together, in a shared decision making model they may weigh risks against the benefits of her being able to extend the use of her implant.

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CHAPTER 3

A Randomized Controlled Trial of Nitrous Oxide for Intrauterine Device
Insertion in Nulliparous Women*Introduction*

Intrauterine devices (IUDs) provide safe, highly effective, and convenient reversible long-term contraception. Despite these advantages, IUDs were used by less than 3.6% of women aged 15–19 years in 2006–2008 in the USA (1). Fear of pain during IUD insertion is a barrier for adolescents and nulliparous women (2). Additionally, clinicians could be reluctant to offer IUDs to nulliparous women, whom they believe experience more pain with IUD insertion (3,4). Because cervical cytology for cancer screening is now deferred until the age of 21 years in the USA (5), and urine testing is often used for sexually transmitted infection screening (6), few young nulliparous women have undergone a pelvic examination. Fear of discomfort associated with such an examination could compound the fear of pain from IUD insertion. Nulliparous women experience moderate pain with IUD insertion (7–9). Misoprostol, non-steroidal anti-inflammatory drugs, and local anesthesia have been studied, but not shown to reduce IUD insertion pain among nulliparous women (10–12). Identification of effective interventions to reduce the pain of IUD insertion for nulliparous women could promote acceptability and utilization.

Nitrous oxide titrated with oxygen (N₂O/O₂) is an inhalation agent that affords safe, effective, non-invasive analgesic and anxiolytic with rapid onset and clearance (13). It has a favorable adverse effects profile, and has been used for many years with excellent outcomes for procedural analgesia and anesthesia in outpatient clinics, including

dentistry and emergency department settings (14–16). N₂O/O₂ is attractive in the clinic because delivery systems are fairly inexpensive, training is not burdensome, and administration of the gas is noninvasive. To our knowledge, no studies have evaluated the use of N₂O/O₂ for IUD insertion among nulliparous women.

The primary objective of the present study was therefore to determine whether N₂O/O₂ at a 50%/50% concentration decreases pain as compared with oxygen alone (O₂) during IUD insertion among nulliparous women who choose a 52-mg levonorgestrel or copper T380A IUD.

Materials and methods

A randomized, double blinded, placebo-controlled trial of N₂O/O₂ versus O₂ for IUD insertion was conducted among nulliparous women attending the Center for Reproductive Health clinic at the University of New Mexico, Albuquerque, NM, USA, between October 1, 2013, and August 31, 2014. English-speaking nulliparous women aged 13–45 years who chose the 52-mg levonorgestrel or copper T380A for contraception were recruited. Women were included if they had never been pregnant or had not carried a pregnancy beyond 19 weeks and 6 days, were at least 4 weeks from the end of a pregnancy, and had a negative urine pregnancy test. Women younger than 18 years were eligible if accompanied by a parent or legal guardian who signed the informed consent. Participants were excluded if they were actively using prescribed opioids, benzodiazepines or illicit drugs, or had contraindications to IUD insertion or N₂O/O₂ administration, including respiratory infection, chronic obstructive pulmonary disease, intoxication, or inability to breathe through the nose. The University of New

Mexico Health Science Center Human Research Review Committee approved the study (ref. no. 13-289) and all participants provided written informed consent before study participation.

Study team members recruited participants on the day of the IUD insertion procedure. Participants received routine clinical and preprocedural care and counseling. After providing informed consent, participants were randomly assigned to one of two groups via a randomization scheme in blocks of four, computer-generated by a statistician not involved in study recruitment. Randomization allocation was concealed in sequentially numbered opaque envelopes. Each envelope was opened by the person administering the inhalation agent immediately before the procedure, and the contents were not seen by other clinicians. A disposable scented nasal mask was fitted for all patients to ensure they were not aware of group assignment. The biostatistician was not masked to group assignment during data analysis.

A dedicated physician or nurse administered N₂O/O₂ or O₂ for 2 minutes, as per the randomization assignment, before the IUD insertion procedure. The N₂O/O₂ delivery system was concealed behind a screen to maintain masking of both the patient and the clinician performing the IUD insertion. N₂O/O₂ was titrated up to a fixed dose ratio of 50%/50% N₂O/O₂ before the IUD procedure; 100% O₂ was used in the control group. The control group did not receive any other medication. Participants were monitored for level of consciousness, ventilation status, and oxygenation during administration of the inhaled gas.

The IUD insertion procedure was similar for all participants. A bimanual examination was performed before speculum insertion. The cervix was cleansed with an

antiseptic solution. A single-tooth tenaculum was placed on the cervix and a uterine sound was used to measure cavity length. The IUD was inserted via a standard insertion technique as described in the package leaflet. The bimanual examination denoted the beginning of the procedure and removal of the speculum marked the end.

The participants assessed their baseline pain, expected pain, IUD insertion pain, and pain at the time of discharge from the clinic via a 100-mm visual analog scale (VAS; 0 mm indicated no pain, 100 mm pain as bad as it can be). The primary pain outcome was maximum pain with IUD insertion assessed 2 minutes after completion of the procedure, which is the timepoint at which N₂O/O₂ is expected to be systemically cleared. Satisfaction with pain management during IUD insertion was assessed with a five-point Likert scale (very satisfied, satisfied, neutral, dissatisfied, and very dissatisfied) and 100-mm VAS (0 mm indicated very dissatisfied, 100 mm very satisfied). Women who reported being dissatisfied were able to describe in free text the reason why they were dissatisfied with their pain management. The physician who inserted the IUD recorded the procedure details and assessed the difficulty of IUD insertion on a 100-mm VAS (0 mm, very easy; 100 mm, most difficult). Physicians were also asked to guess whether the patient had received N₂O/O₂ or 100% O₂. Participants completed a demographic and medical history questionnaire before the procedure. Before discharge from the clinic, women also completed a questionnaire regarding their IUD insertion experience, which included a question asking them to guess whether they had received N₂O/O₂ or 100% O₂. All participants received a US\$10 gift card for a local retail shop to compensate for the inconvenience of the study procedures.

Sample size was based on the assumption that a 15-mm difference on a 100-mm

VAS is the minimal clinically important difference in pain (17). In previous studies, mean pain scores (measured on a 100-mm VAS) for IUD insertion among nulliparous Hispanic and non-Hispanic white women were 61.9 ± 25 mm (8) and 55 ± 21 mm (7), respectively. Because the New Mexico population consists of primarily non-Hispanic white and Hispanic women, a pooled standard deviation (SD) of 23 was assumed. To detect a 15-mm difference in pain scores between the N₂O/O₂ and O₂ groups with an SD of 23, a sample size of 38 women per treatment group was necessary with a β value of 0.80 and an α value of 0.05. With an anticipated 5% drop out rate after randomization, the recruitment goal was established at 40 women per group.

Study data were collected and managed using Research Electronic Data Capture (REDCap) (18). Different research coordinators entered the study data into the Double Data entry feature in REDCap to compare data entry results via the data comparison tool. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for all data analyses.

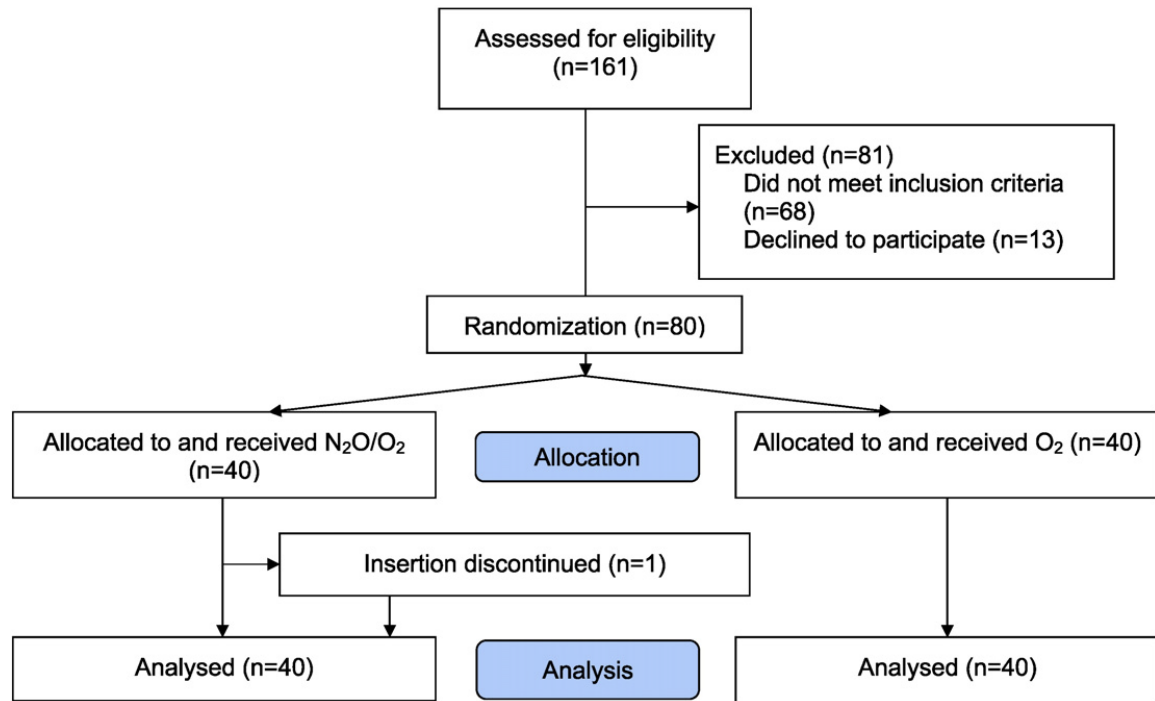
Data were analyzed by intention to treat. Normally distributed continuous variables were compared by parametric tests (t test and analysis of variance), and continuous variables that were not normally distributed were compared by non-parametric Wilcoxon-rank sum tests. Categorical variables were compared by Fisher exact test. $P < 0.05$ was considered to be statistically significant.

Results

Among 161 women evaluated for enrollment, 93 (58%) were eligible (Figure 1). Of the 93 eligible women, 80 (86%) were enrolled; 40 were allocated to each group. The IUD insertion procedure was discontinued for one participant in the N₂O/O₂ group

owing to the creation of a false tract, but she was included in the analysis (Figure 1).

Fig. 1. Flow of patients through the study.



The mean age of participants was 25.6 ± 5.8 years. Most women were single (52 [65%] participants), and were predominantly non-Hispanic white (43 [54%]) and Hispanic (29 [36%]). Most women had completed some college or were college graduates (73 [91%]), and most were employed either part- or full-time (63 [79%]). Most participants earned less than US\$40 000 per year (51 [64%]). Characteristics of women in the N2O/O2 group were similar to those of the participants assigned to the O2 group (Table 1).

Table 1
Baseline characteristics.^a

Characteristic	N ₂ O/O ₂ (n=40)	O ₂ (n=40)
Age, y	24.9 ± 5.9	26.3 ± 5.6
Nulligravid	33 (83)	30 (75)
Prior sexually transmitted infections	6 (15)	11 (28)
Race		
Non-Hispanic white	24 (60)	19 (48)
Hispanic	14 (35)	15 (38)
Other	2 (5)	6 (15)
Marital status		
Single ^b	32 (80)	25 (63)
Married/living with partner	8 (20)	15 (38)
Education		
No college	5 (13)	2 (5)
In college/some college	14 (35)	20 (50)
Graduated from college	21 (53)	18 (45)
Employment status		
Part-time	12 (30)	11 (28)
Full-time	18 (45)	22 (55)
Unemployed/disability	10 (25)	7 (18)
Household income, US\$		
<20 000	16 (40)	12 (30)
20 001–40 000	12 (30)	11 (28)
40 000	12 (30)	17 (43)
Type of IUD		
Levonorgestrel 52 mg ^c	34 (85)	33 (83)
Copper T380A IUD	5 (13)	7 (18)
Pre-procedure self-medication	12 (30)	10 (25)
IUD removal/reinsertion	3 (8)	7 (18)

Abbreviation: IUD, intrauterine device.

^a Values are given as mean ± SD or number (percentage).

^b Including divorced, separated, and widowed.

^c One patient had an unsuccessful insertion.

Mean insertion pain scores at IUD insertion were similar among the N₂O/O₂ and O₂ groups (P=0.86) (Table 2). Baseline and expected pain, and pain at the time of discharge from the clinic were also similar between the two groups (Table 2). The 52-mg levonorgestrel IUD was selected by 67 (84%) participants. Mean insertion pain score was 57.5 ± 21.7 mm with the 52-mg levonorgestrel IUD and 43.4 ± 23.0 mm with the copper T380A IUD (P=0.07).

Table 2
Pain and satisfaction scores.^a

Outcome	N ₂ O/O ₂ (n=40)	O ₂ (n=40)	P value
Baseline pain, mm ^b	2.4 ± 4.1	1.9 ± 4.6	0.64
Expected pain, mm ^b	53.1 ± 23.3	56.4 ± 18.9	0.49
Insertion pain 2 minutes after the procedure, mm ^b	54.3 ± 24.8	55.3 ± 20.9	0.86
Pain at time of discharge, mm ^b	19.1 ± 17.4	19.0 ± 17.6	0.99
Satisfaction, mm ^b	66.0 ± 32.2	60.3 ± 26.6	0.39
Satisfaction			0.04
Satisfied/very satisfied	27 (68)	17 (43)	
Neutral/dissatisfied/very dissatisfied	13 (33)	23 (58)	

^a Values are given as mean ± SD or number (percentage), unless indicated otherwise.

^b By 100-mm visual analog scale for pain and satisfaction.

Use of adjunctive measures—e.g. the os-finder and dilators—was more common in the N₂O/O₂ group than in the O₂ group (P=0.02), whereas the procedure duration did not differ between the two groups (P=0.14) (Table 3). The obstetrics–gynecology faculty, family medicine faculty, and family planning fellows inserted all IUDs, with most inserted by the obstetrics–gynecology faculty (46 [58%]). Pain scores did not differ among the provider types (data not shown). One (3%) IUD insertion procedure was unsuccessful within the N₂O/O₂ group owing to the creation of a false tract.

Table 3
Procedure characteristics by study group allocation.^a

Characteristic	N ₂ O/O ₂ (n = 40)	O ₂ (n = 40)	P value
Use of adjunctive measures	14 (35)	8 (20)	0.02
Ultrasonography	5 (13)	2 (5)	0.26
Procedure duration, min	4.56 ± 3.6	3.60 ± 1.8	0.14
Provider ^b			0.68
Ob/Gyn faculty	24 (60)	21 (54)	
Ob/Gyn fellow	9 (23)	8 (21)	
Family medicine faculty	7 (18)	10 (26)	
Provider ease of insertion ^c	25.2 ± 25.1	17.8 ± 19.3	0.16
Adverse effects	6 (15)	7 (18)	0.32

^a Values are given as number (percentage) or mean ± SD, unless indicated otherwise.

^b Data not available for one patient in the O₂ group.

^c By 100-mm visual analog scale for provider ease of insertion.

Satisfaction with pain management was similar between the N₂O/O₂ and O₂ groups (P=0.39) (Table 2). Significantly more women in the N₂O/O₂ group than in the O₂ group were satisfied with their pain management on the Likert scale (P=0.04) (Table 2). Women reported their dissatisfaction with pain management as follows: “It hurt more than I expected;” “There needs to be better options for pain management;” and “I felt there was little to no pain control.”

The frequency of adverse effects did not differ by group (P=0.32) (Table 3). Three (8%) women in the N₂O/O₂ group experienced dizziness, and 5 (13%) in the O₂ group reported nausea.

Irrespective of the randomization group, most women reported that they would choose an IUD for contraception again in the future, and most would choose N₂O/O₂ for pain management during the insertion procedure (data not shown). Notwithstanding the discomfort of the procedure and irrespective of group, most women would also recommend the IUD to a friend and would recommend N₂O/O₂ for IUD insertion (data

not shown). Overall, 50 (63%) participants reported that they would be willing to pay an additional US\$20–\$50 to receive N₂O/O₂ during the insertion procedure.

Physicians correctly identified the gas assignment for approximately 19 (48%) women receiving N₂O/O₂ and 24 (60%) of those receiving O₂. Most women in the O₂ group (38 [95%]) correctly identified receiving O₂, and only half (21 [53%]) correctly identified receiving N₂O/O₂.

Discussion

In the present study, nulliparous women experienced pain with IUD insertion, and inhaled N₂O/O₂ made the participants more satisfied with the insertion process although their pain was not reduced. The finding of no reduction in pain with N₂O/O₂ could reflect the use of a suboptimal concentration of N₂O/O₂, which was fixed at 50% N₂O and 50% O₂. One distinct advantage of N₂O/O₂ is that it can be titrated in incremental doses quickly until a patient has reached a comfortable, relaxed state of sedation. By using a fixed proportion, the dosing of N₂O/O₂ was not optimized to the individual patient needs. The N₂O/O₂ delivery system that was used includes a scavenging vacuum system on the mask, which might also negatively affect the concentration of gases delivered. For a brief gynecologic procedure lasting only a few minutes, a higher ratio—e.g. 70%/30% N₂O/O₂, as used for dental procedures—might be more effective.

The primary outcome of the study was assessed at 2 minutes after the procedure when the effects of N₂O/O₂ would have dissipated. Past experience using N₂O/O₂ at the study institution has indicated that an assessment of pain during IUD insertion while the patient is under the influence of N₂O/O₂ could yield different results.

The signs and symptoms of N2O/O2 sedation are very apparent and therefore could have affected the ability of the outcome assessors to be truly masked to the patient's intervention assignment. The present results suggest that physicians and participants correctly identified participants receiving N2O/O2 in slightly more than 50% of cases.

Women who received N2O/O2 were more satisfied with their pain management. This finding is consistent with the manner in which N2O/O2 works as an analgesic (via mediation of release of endogenous opioids) (19) and anxiolytic (via modulation of GABA receptors) (20). A similar finding of increased patient satisfaction with pain management, despite an insignificant reduction in pain, has also been demonstrated when N2O/O2 is used for labor analgesia (21) and for first-trimester surgical abortion (22).

The strengths of the study include the double-blind, placebo controlled, randomized design; the ethnic diversity of the participants; and the use of N2O/O2 as an intervention. Once the initial expense of installing a N2O/O2 system has been met, the ongoing costs of N2O/O2 administration and training are manageable for small clinics. Furthermore, N2O/O2 has minimal adverse effects and quickly dissipates from the body, obviating the need for post-procedure monitoring.

The limitations of the study include limited external generalizability, fixed dosing of N2O/O2, and use at a high altitude (Albuquerque is approximately 1600 m above sea level), which decreases the effect of N2O/O2. Other limitations could include timing of pain assessment, and limited ability to truly mask outcome assessors and patients to the effects of N2O/O2. The study was conducted at an academic family planning center

where all insertions were performed by faculty and family planning fellows who frequently insert IUDs in nulliparous women. Overall, the IUD insertion pain scores in the study were lower than those reported in other studies (7,8).

In conclusion, women desire an intervention to help reduce the pain of IUD insertion and, on the basis of the present study, N₂O/O₂ has the potential to improve the experience of pain by increasing satisfaction with pain management. Higher concentrations of N₂O and titration of the ratio to an individual's needs could further improve the experience of nulliparous women with IUD placement. It could also be valuable to explore N₂O/O₂ for pain management of other office-based gynecologic procedures.

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CHAPTER 4

Nitrous Oxide versus Intravenous Sedation for Anesthesia: A Randomized Clinical Trial

Introduction

Pain management is an important component of patient-centered abortion care. Of the estimated annual 926,200 abortions in the United States, 96% occur in the office setting with limited anesthesia options (1). Second trimester abortion is painful and commonly performed with use of intravenous (IV) sedation with midazolam and fentanyl for analgesia (2). Data is sparse about what constitutes an ideal anesthetic for this procedure. Many clinics administering IV sedation require women to fast prior to the procedure and bring a chaperone to drive them home, (3) a burdensome requirement for women who may travel long distances and need or desire to maintain privacy. The ideal anesthetic for second trimester abortion would effectively control abortion pain, maintain patient safety, be easily administered, and have rapid onset and clearance.

Nitrous oxide (N₂O/O₂) offers analgesia, anxiolysis and amnesia, has immediate onset of action and dissipates rapidly (4)(5)(6). Its safety and efficacy have been established for dentistry, emergency department procedures and vaginal delivery (7)(8). Few studies have examined nitrous oxide for sedation in outpatient gynecologic procedures. Prior research has not found pain reduction in first trimester abortion when utilizing nitrous oxide as an adjuvant treatment at lower concentrations (9)(10). However, one prior study evaluated nitrous oxide alone at an increased titration schedule (70% nitrous:30% oxygen) compared to oral sedation for first trimester surgical abortion with similar mean pain scores (11). In the setting of transcervical sterilization procedures, nitrous oxide has been shown to be superior to oral sedation (12).

In this multisite, double blinded, randomized clinical trial, we investigated whether nitrous oxide was a non-inferior alternative to IV sedation for pain management in surgical abortion between 12 and 16 weeks. Our primary outcome was the difference between the groups in maximum abortion pain, measured as means on a Visual Analog Scale (VAS). We hypothesized that the VAS pain scores of participants receiving nitrous oxide would be non-inferior to those of participants receiving IV sedation.

Materials and Methods

From August 2016 to March 2017, eligible women were recruited from the University of New Mexico and the University of Colorado reproductive health clinics. These are both University-based clinical practices with a focus on complex contraception and abortion care and are responsible for training Ob/Gyn family planning fellows.

Eligible women were over age 18, between 12 and 16 weeks gestational age by best obstetrical dating, English or Spanish speaking, and able to obtain a ride home following the procedure. Exclusion criteria were clinical contraindications to outpatient abortion such as invasive placentation or significant medical comorbidities, or contraindications to nitrous oxide such as active upper respiratory tract infection, chronic obstructive pulmonary disease and current treatment with bleomycin chemotherapy. Additional exclusion criteria were intrauterine fetal demise, chronic narcotic use or prior adverse reactions to any of the study drugs. Microsoft Excel was utilized to create a randomization list with a block randomization scheme and stratification by gestational age in weeks.

After women decided to proceed with outpatient abortion and gave appropriate informed consent, research staff approached and enrolled prospective participants. Cervical preparation occurred at the treating physician's discretion and included intracervical dilators and/or misoprostol. Participants were randomized to IV sedation or nitrous oxide immediately prior to the abortion procedure. The anesthesia provider opened the appropriate opaque envelope to determine the allocation. All participants received 600mg of ibuprofen, IV access and a scented face mask worn for the duration of the procedure. Participants were positioned for the procedure and the unblinded anesthesia provider administered allocated study medications at least two minutes prior to starting the procedure. The IV sedation group received 100 mcg of fentanyl and 2 mg midazolam IV, and 100% oxygen via face mask; those allocated to nitrous oxide received IV saline, and were titrated to 70% nitrous oxide:30% oxygen via face mask. All participants received a standardized paracervical block of 20 cc of buffered lidocaine, with 1-2 cc at the tenaculum site, and 18 cc divided equally at the 4 and 8 o'clock cervicovaginal junction (13). If a participant needed further pain medication during the procedure, based on participant response or physician assessment, those in the IV sedation group received additional IV sedation medications and those in the nitrous oxide group received 100 mcg of fentanyl and 2 mg midazolam IV after discontinuation of the nitrous oxide and more IV sedation medications as needed according to clinic protocol. In the event of over-sedation, all members of the team were to be unblinded and appropriate resuscitative measures initiated.

The abortion procedure technique followed clinical standard of care, and was not altered for the study; details of the procedure including duration, use of mechanical

dilation, cannula size and use of forceps was recorded. Immediately following the procedure and while still receiving the allocated medication, participants rated their maximum pain on the VAS. Following the procedure, nurses monitored participants until they achieved an Alderete score of 8 or greater (14). At 30 minutes post-procedure, participants completed another VAS, recalling maximum abortion pain. To maintain masking, all procedural data were entered into a Research Electronic Data Capture (RedCap) database (15) by study coordinators, while medication information was entered separately by the anesthesia provider or research pharmacist.

The primary study outcome was immediate recall of maximum procedural pain on the VAS. In the only study of pain during second trimester abortion, median pain for expulsion of the fetus during medical induction with or without IV fentanyl was 70mm (IQR 50, 80) (16). We used this value to calculate sample size using a 1-sided, 2-group test of non-inferiority and determined that a sample size of 76 participants with 38 per treatment group, could detect a non-inferiority margin of 15mm with 90% power and type 1 error of 5%.

A data safety monitoring board (DSMB) was created along with pre-determined study stopping rules. This DSMB of external reviewers knowledgeable in family planning and abortion care, not involved in the study, planned to review data after each quarter of participants was enrolled. Prior clinical data from the University of Colorado demonstrated that 24% (+/-7% [CI 95%]) of women undergoing abortion in our target gestational age received additional IV pain medication. Based on this percentage, we created a stopping rule to halt the study and conduct a full data and safety review if more than 35% of women in either group required additional pain medication.

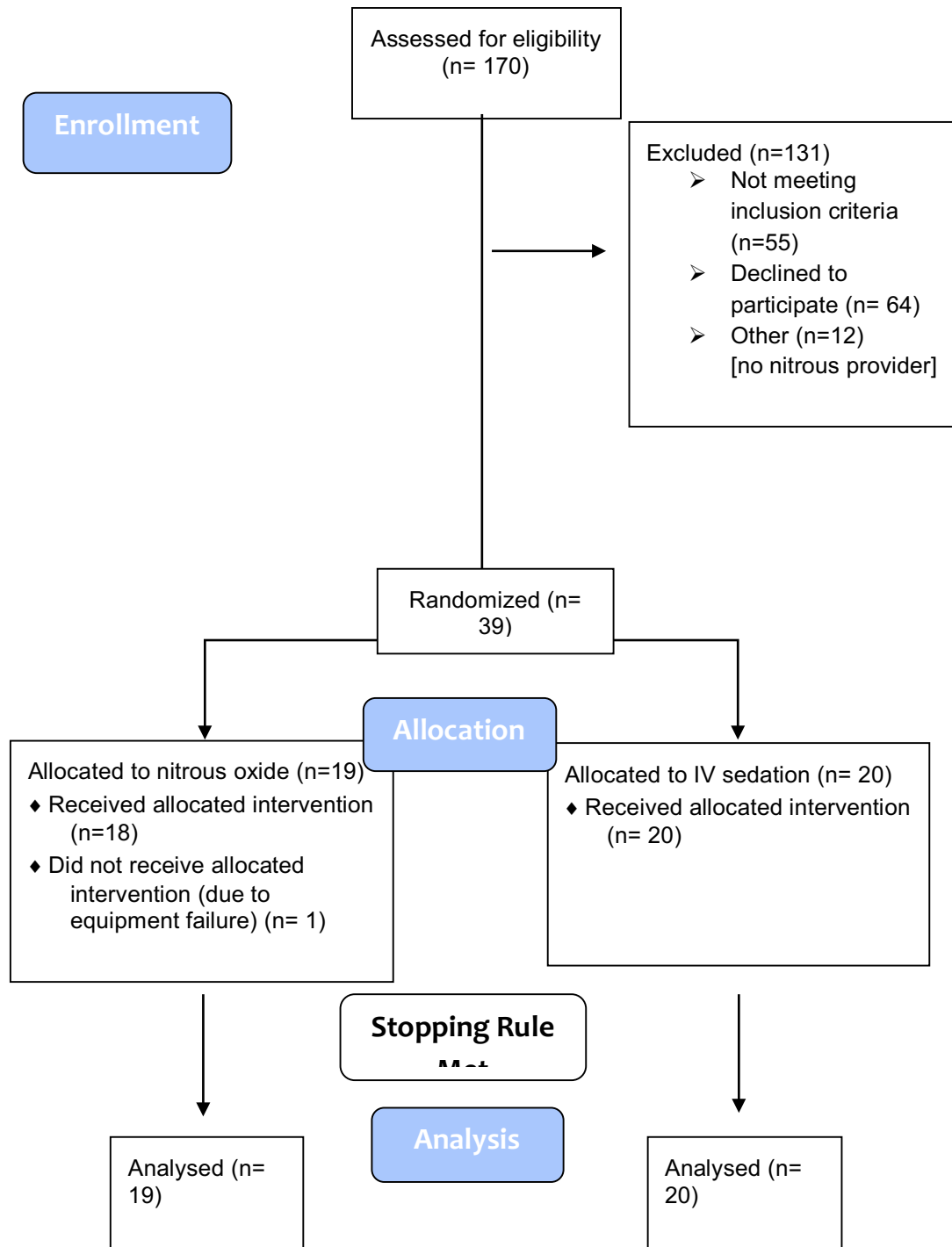
Nonparametric Wilcoxon rank sum tests were used for non-normally distributed continuous data, tests of proportions were used to assess binomial outcomes and Pearson χ^2 tests were used for categorical variables. Both intention-to-treat (ITT) and per protocol analysis were performed with per-protocol analyses only reported if findings were different from ITT (17) (18). Women requiring additional pain medication were then considered a separate group and median pain scores analyzed by one way Kruskal-Wallis test. Sample size calculations were performed and data were analyzed using STATA/SE 14.1 (2015), StataCorp LP, College Station, TX, USA.

The institutional review boards at the University of New Mexico Health Sciences Center and the University of Colorado approved this study.

Results

Of 170 participants assessed for eligibility, 39 were enrolled and randomized: 19 to the nitrous group and 20 to the IV sedation group. Eligibility was assessed and is reported per CONSORT guidelines (Figure 1). One participant within the nitrous group did not receive her allocated intervention due to equipment failure. No women in the IV sedation group required additional pain medications. Seven women in the nitrous group (37%) underwent conversion to IV sedation because they required additional pain medication, as determined by the patient and/or the physician. This percentage exceeded our predefined stopping rule of 35%. Enrollment was halted by the DSMB and data were analyzed.

Figure 1: Study Flow Diagram



Baseline participant demographic and procedural characteristics were similar between the two study groups (Tables 1 and 2). The median age of the cohort was 26 years (range 18-42 years), and just over half of women were parous. Participants represented a diversity of ethnicities consistent with the populations of the two study sites. Participants were recruited evenly from both locations and almost all procedures were performed by an Ob/Gyn attending physician or family planning fellow (95% nitrous group, 95% IV sedation group). Most procedures required cervical preparation with misoprostol, osmotic dilators, or both and most were completed on the same day (84% nitrous group, 78% IV sedation group).

Table 1: Baseline Participant Characteristics

Characteristics	N₂O/O₂ N= 19 (frequency, %)	IV Sedation N = 20 (frequency, %)
Age (yrs)*	27 (22, 34)	26 (20, 29)
Prior birth outcomes‡		
Vaginal Births	10 (53)	11 (55)
C-Section Births	6 (34)	2 (10)
Abortions	7 (37)	5 (25)
Miscarriages	5 (26)	8 (40)
Stillbirth	1 (5)	0 (0)
None (Nulliparity)	3 (16)	8 (40)
Ethnicity		
Hispanic	10 (53)	9 (45)
Race		
White	8 (42)	8 (40)
Black or African American	4 (21)	0 (0)
American Indian/Alaska Native	1 (5)	3 (15)
Other including mixed	6 (32)	9 (45)
Relationship status		
In a committed relationship	13 (68)	13 (65)
Education		
High school or equivalent	8 (42)	8 (40)
More than high school	8 (42)	9 (45)
Bachelor's or graduate degree	3 (16)	2 (15)
Gestational age		
12	8 (42)	8 (40)
13	3 (16)	4 (20)
14	5 (26)	5 (25)
15	3 (16)	3 (15)

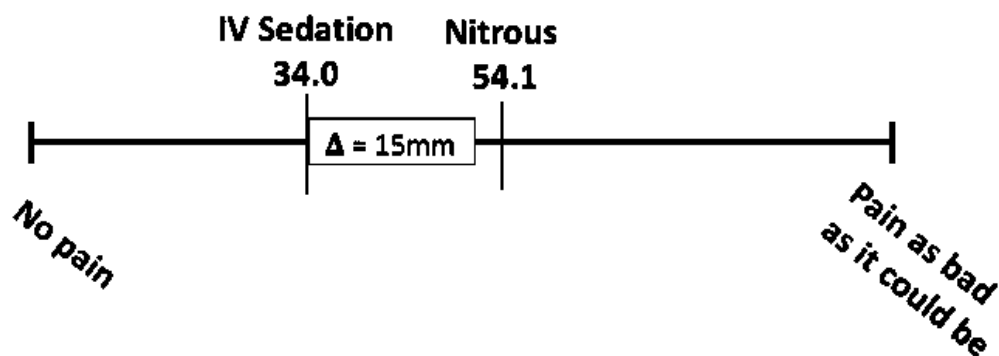
*Age reported in Median (Interquartile range).

‡Values do not total to 100% to reflect multiple birth outcomes per participant.

Table 2: Procedure Information

Characteristic	N ₂ O/O ₂ N= 19 (frequency, %)	IV Sedation N = 20 (frequency, %)
Provider		
Ob/Gyn Attending	7 (37)	10 (50)
Family Practice Attending	1 (5)	1 (5)
Family Planning Fellow	11 (58)	9 (45)
Location		
UNM	11 (58)	12 (60)
CO	8 (42)	8 (40)
Cervical prep		
Misoprostol	15 (79)	13 (76)
Osmotic dilators	5 (26)	8 (40)
Length of prep		
One day	16 (84)	14 (78)

In intent-to-treat analysis, immediate VAS pain scores were analyzed using least squares means to prove inferiority: pain scores were lower among women randomized to IV sedation by 20.1 mm (95% CI 1.6 to 38.6), a value which is beyond our a priori inferiority margin of 15 mm (Figure 2).

Figure 2: Mean Maximum Procedural Pain (along the VAS in mm)

In per-protocol analysis, this effect was no longer significant. In order to separate and evaluate the pain scores of those women that had been converted from nitrous to IV

sedation, the groups were then divided into three categories: IV sedation, nitrous sedation and those that were converted to IV sedation. Due to the small size of the populations and non-normal distributions, nonparametric analysis was performed with immediate post-abortion median (Q1, Q3) pain scores of 29 mm (16, 49), 30 mm (15, 78) and 67 mm (60, 75) respectively ($p < 0.05$) (Figure 3).

Figure 3: Maximum Procedure Pain

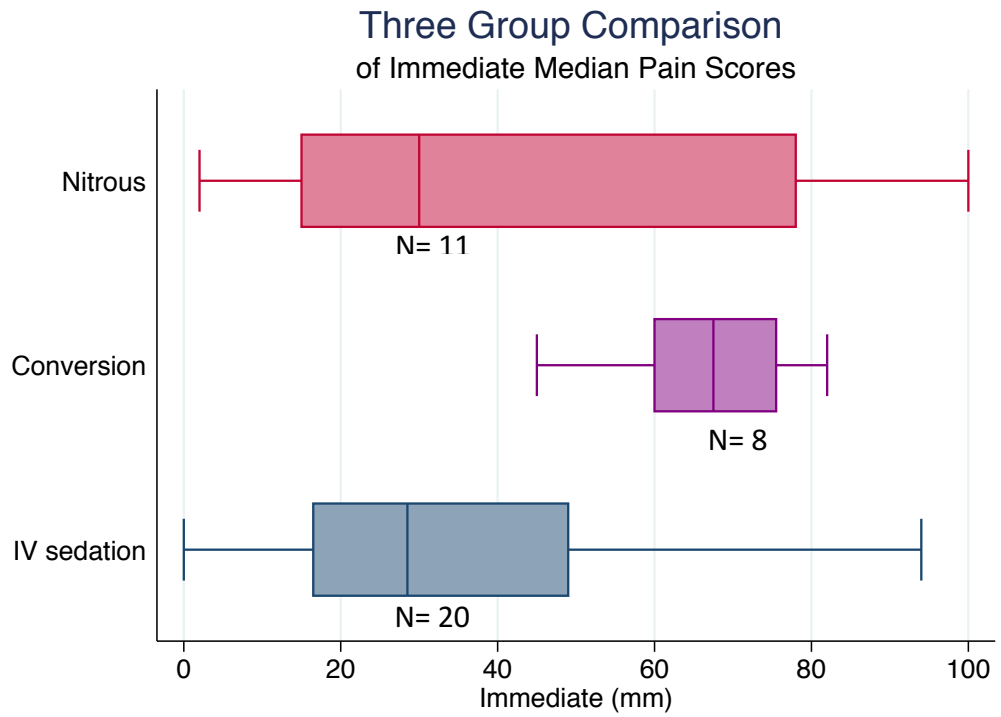


Table 3: Pain Scores (as reported by VAS in mm)

Pain Time point	N₂O/O₂ N = 19 (median, IQR)	IV Sedation N = 20 (median, IQR)	p-value
Baseline	3 (1, 11)	2 (0, 22)	NS
Expected	49 (35, 78)	54 (20, 70)	NS
Maximum experienced (immediate recall)	61 (30, 78)	28 (16, 49)	0.03
Maximum experienced* (recall prior to leaving clinic)	66 (38, 88)	17 (6, 40)	0.001

*N=18 in N₂O/O₂ group

Similar to immediate post-abortion pain scores, the median (Q1, Q3) VAS scores for recall of maximum abortion pain prior to discharge from the clinic were lower among women randomized to IV sedation; 66 mm (38, 88) in the nitrous group, and 17 mm (6, 40) in the IV sedation group (Table 3). Duration of the procedure was longer among women randomized to nitrous oxide: 14 minutes (11, 17) in the nitrous group, and 10 minutes (8, 12) in the IV sedation group. When analyzed by allocation received, it became apparent that the longer times were due to conversion from nitrous to IV sedation. Participants reported few side effects; one noted nausea and five bled to the point of requiring additional medications (not different between groups). No women in either group became over sedated.

Discussion

Under our experimental conditions, nitrous oxide was inferior to IV sedation for pain control in 12-16 week abortion care. Few women experienced side effects of nitrous oxide and no women became over sedated.

We chose to investigate nitrous oxide as an anesthetic agent for this procedure because of perceived benefits to both clinics and patients. Nitrous oxide is an appealing agent for use in the clinic as delivery systems are relatively inexpensive and training is not burdensome. Benefits to the patient include rapid reversibility with administration of 100% oxygen and noninvasive delivery of the gas (5)(6). When evaluating the quality of the abortion care experience, women value both pain control and privacy (19); an effective rapidly reversible medication provides both.

Strengths of this study included its randomized controlled design with multi-site recruitment. We used validated metrics to evaluate pain with anesthesia. Limitations of the study included use of nitrous oxide in the high altitude cities of Albuquerque and Denver, where the analgesic effect may be reduced (20). Additionally, pain scores from prior studies was not consistent with pain scores identified in this study. Our assumptions were based on second trimester medical pregnancy termination with IV fentanyl, (16) since no studies had established mean pain scores among women during a second trimester surgical abortion procedure. Pain scores for second trimester surgical abortion in this study were much lower than those reported with medical termination of pregnancy.

We found nitrous oxide to be an inferior method of anesthesia compared to IV sedation for 12-16 week surgical abortion, however future studies should continue to search for a patient-centered quality anesthetic to provide alternative options for women.

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CONCLUSION

The enclosed primary studies were designed to investigate avenues for improving the delivery of family planning care per the Institute of Medicine's quality principles. Through systematic review of the existing literature, there is not sufficient evidence to change recommendations for contraceptive implant duration for all women. However, young, healthy women of normal body mass index should have the opportunity to extend use in consultation with their provider. This information is currently under review with the World Health Organization (WHO) and providers should await their final recommendations for further guidance. Nitrous oxide did not improve the experience of pain with IUD insertion or second trimester abortion. This method of anesthesia was chosen for its rapid clearance, allowing women to fit family planning care into their daily lives with convenience and confidentiality. Future studies should investigate novel anesthetic agents with similar rapid clearance properties. While there is still much to be learned about the medical community's ability to increase the quality of care rendered, these studies add to the growing body of literature on patient-centered health care delivery.