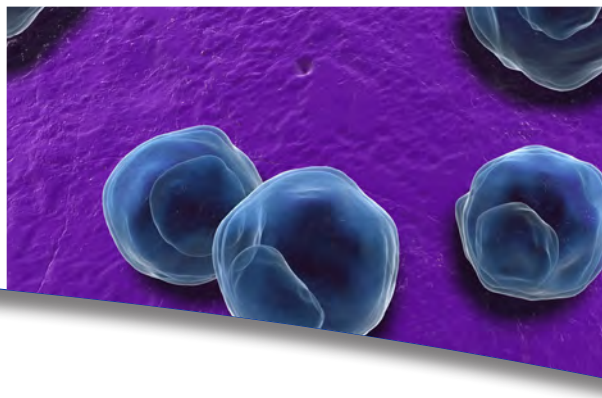
National Public Health Action Plan

for the Detection, Prevention, and Management of Infertility



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This publication addresses the public health importance of infertility and challenges as well as opportunities for action. The findings and recommendations contained in this publication may serve as a platform to stimulate discussion and collaboration among Federal agencies, professional organizations, academic institutions, and those who represent consumers of health services.

Contents

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Executive Summary

Because the desire to have one's own biological children can be strong and compelling, the effects of infertility for individuals or couples who are unable to conceive can be devastating. Infertility or its treatment can cause psychological stress, anxiety, and depression. Treatment of infertility can be medically invasive and may cause discomfort or, in some cases, be associated with health problems for women, men, and the resulting children. Given the goal of public health is to reduce disease, premature death, injury, and disability through prevention and health promotion, preventing infertility and the adverse consequences associated with its treatment are important concerns. A clear need exists to identify public health priorities regarding infertility and its effect on health.

Infertility may be caused by a myriad of factors including genetic abnormalities, aging, acute and chronic diseases, treatments for certain conditions, behavioral factors, and exposure to environmental, occupational, and infectious agents. However, many questions about infertility remain unanswered. In addition, significant disparities exist by race, ethnicity, sex, and socioeconomic status in the prevalence, diagnosis, referral, and treatment of infertility. Furthermore, treatments for infertility can carry health risks for women, men, and their children. This publication addresses these issues, focusing on the public health aspects of infertility detection, prevention, and management.

Description of the National Public Health Action Plan

In consultation with many governmental and nongovernmental partners, the Centers for Disease Control and Prevention (CDC) developed the *National Public Health Action Plan for the Detection, Prevention, and Management of Infertility* (hereafter called the *National Action Plan* or the *Plan*). This plan highlights the need to better understand and address issues at a population level that contribute to and are caused by infertility in women and men and that may affect the health of the pregnancy.

Specifically, this plan focuses on:

1. Promoting healthy behaviors that can help maintain and preserve fertility.
2. Promoting prevention, early detection, and treatment of medical conditions that can threaten fertility.
3. Reducing exposures to environmental, occupational, infectious, and iatrogenic agents that can threaten fertility.

Because of its public health focus, these strategies also call for promoting healthy pregnancy outcomes associated with treating and managing infertility and improving the safety and efficacy of infertility treatments.

Introduction

In general, infertility refers to the inability of couples to conceive a clinical pregnancy after 1 year or more of trying.[1] However, definitions for infertility vary widely depending on the type of information available and the purpose for which the information is collected.[2] For example, some clinical definitions of infertility include women aged 35 years or older after 6 months of trying to conceive. Further delaying the initiation of infertility interventions could limit their effectiveness. In contrast, demographic definitions of infertility often encompass the inability to have a live birth among sexually active women who are not using contraception. These definitions better meet the needs and constraints of demographic research because of the difficulty in collecting complete information about conception, particularly in studies conducted in developing nations.[3] Regardless, the true burden of infertility may be underestimated because neither definition necessarily reflects people who may have stopped trying or who have experienced infertility in the past.

Infertility can take several different forms, including *resolved infertility* (pregnancies that occur after 1 year of trying without medical intervention), *primary infertility* (never pregnant), or *secondary infertility* (failure to conceive after having previously delivered an infant without the use of infertility treatment). Other conditions related to infertility are also important to consider when assessing the effect of infertility on public health. *Fecundability* refers to the probability of becoming pregnant in a single menstrual cycle, conditional on not being pregnant in the previous cycle.[3] *Impaired fecundity* has been defined as physical difficulty in getting pregnant or carrying a pregnancy to term birth.[4] Because this publication draws on many different sources of information regarding infertility, we use these terms broadly and cite references for more specific definitions as needed.

Public Health Priority

Although the ability to have children is often assumed, a significant proportion of individuals and couples experience infertility and may be affected by its resulting social, economic, psychological, and physical effects. The ability to have children represents more than a quality-of-life issue. The World Health Organization (WHO) and other professional organizations, such as the American Society for Reproductive Medicine, have defined infertility as a disease.[1,5] Early environmental, chemical, or occupational exposures (e.g., *in utero*, in childhood) could permanently change fecundity or biologic capacity by affecting gynecologic, urologic, or pregnancy health. These exposures could also affect fertility outcomes (e.g., multiple births, prematurity) and increase the likelihood of later adult-onset diseases, such as ovarian, testicular, or prostate cancers,[6-9] metabolic syndrome, and polycystic ovary syndrome. In this way, infertility may serve as a marker of past, present, and future health and provide a window of opportunity to improve care for affected reproductive-aged women and men. Thus, infertility could have public health implications beyond simply the ability to have children.

Infertility affects a substantial percentage of reproductive-aged women and men in the United States. One approach to estimating infertility considers the entire population of women and men of reproductive age, regardless of current fertility intentions. Nationally representative data using this approach have come from CDC's National Survey of Family Growth (NSFG) dating back to the early 1980s; the most recent data from the 2006–2010 survey show that, among all married US women aged 15–44 years, 6.0% or an estimated 1.5 million women (and thus their husbands) were infertile and 12% (or 3.1 million women) had impaired fecundity.[4] A second approach to estimating infertility considers only the population of reproductive-aged women (and their partners) at risk for infertility, such as those who are actively trying to become pregnant. Studies using this approach have generally yielded higher estimates of infertility. A review of previous US studies, most of which were small and not nationally representative, for example, suggested as many as 12%–18% of couples do not achieve pregnancy within 12 months or cycles of trying.[10] Estimates from earlier, nationally representative data from the 2002 NSFG among a similar population of women (and their partners) who were trying to become pregnant indicate that a comparable proportion (16%) were infertile.[10,11]

For males, some form of infertility was reported by 9% of men, again according to CDC's NSFG conducted from 2006–2010.[4] As with women, the percentage of men reporting infertility was higher when assessing those couples who were trying to become pregnant. Estimates from the earlier NSFG sample of males from 2002, for example, suggest that 12% of couples may be affected by infertility.[12]

Environmental and occupational hazards account for an unknown proportion of male infertility but are suspected causes of declining human sperm quality in industrialized countries.[13-15] The proportion of infertility cases attributable to male-specific factors may be substantial. One earlier evaluation conducted in developed countries in the 1980s by WHO found that 8% of infertility cases were attributable to male factors and 35% to both male and female factors, whereas 37% were attributable to female factors alone and 5% to an unknown cause (the remaining 15% of women became pregnant).[16] Another evaluation estimated that male factors account for approximately 20% of couple infertility, with another 30%–40% of cases attributable to reproductive abnormalities that were present in both partners.[17]

The natural age limits of fertility in both women and men have become more apparent with the recent trend toward delaying childbearing in the United States.[18-21] The percentage of first births among women aged 30 years or older increased from 5% in 1975 to 26% in 2010.[22,23] Infertility also remains closely associated with age, especially for nulliparous (i.e., childless) women. Recent data from the NSFG, for instance, indicate that among nulliparous women, the percentage experiencing infertility increases markedly with age, from 7%–9% among those aged 15–34 years to 25% among those aged 35–39 years and 30% among those aged 40–44 years.[4] As women age, the risk of infertility rises because of diminished egg quality and ovulatory function and because of an increased risk of disorders such as endometriosis, leiomyomata, and tubal disease.[24] Advanced paternal age also might contribute to infertility through reductions in the quality and quantity of sperm produced.[20,21,25] The combination of the high proportion of pregnancies in the United States that are unintended (about 50%)[26] and the rise in intended pregnancy at later ages, when infertility is increasingly common, indicates a basic need for improved education on family planning, infertility, and other reproductive health issues for people who may want children in the future.

In the United States, data from the 2006–2010 NSFG [27] also show:

- 12% of women of reproductive age (7.3 million women), or their husbands or partners, had ever used infertility services in their lifetime
- The percentage of women seeking such services increased with age and was approximately 20% among women aged 35–44 years
- About 9% of sexually experienced US men aged 25–44 years reported they or their wives or partners had ever used infertility services to help have a child

Services and treatments for infertility range from counseling and advice to medications and surgery. The most common medical services received by reproductive-aged women with current infertility problems were those at the lower end of cost and complexity including advice (29%), testing of her or her male partner (27%), and ovulation medications (20%). Less commonly received services included intrauterine insemination (IUI) (7%), surgery or treatment for blocked tubes (3%), and assisted reproductive technology (ART) (3%).

Treatments for infertility can carry significant health risks to the mother and child. For example, a very rare but serious risk of using drugs for ovulation induction is ovarian hyperstimulation syndrome (OHSS), which is characterized by enlargement of the ovary and an accumulation of fluid in the abdomen.[28] OHSS is usually self-limiting, resolving spontaneously within several days, though the most severe cases may require hospitalization and intensive care. In addition, some (but not all) research suggests that infertility treatments may be associated with an increased risk of gynecologic or breast cancer.[29,30] Infertility treatments have increased the rate of twin and higher-order multiple births, which put both mother and infants at higher risk of adverse health outcomes.[31-33] Even singleton births resulting from ART are associated with increased risk of low birth weight (<2,500 grams).[34] Infants who are born to mothers who receive ART[35,36] or non-ART (e.g., clomiphene citrate)[37] treatments may be at higher risk of birth defects.

Overall, the long-term health risks for women and men receiving treatment for infertility and for children born as a result of ART or other treatments are not known.[38]

Development of the National Public Health Action Plan

In 2007, a CDC-wide ad hoc work group was formed to examine the full scope of infertility activities across the agency. This work group conducted an assessment to identify gaps and opportunities in public health surveillance, research, communications, programs, and policy development. This assessment led to publication of a White Paper outlining the need for a national plan with a public health focus on infertility prevention, detection, and management.[39] In September 2008, CDC also hosted a symposium "Infertility as a Public Health Issue" attended by about 60 stakeholders from Federal agencies, professional and consumer organizations, academia, and the health care community.

In response to interest from Congress[40] and stakeholders, CDC developed this National Action Plan to promote collaborative activities within and outside the Federal government. A draft of the document was posted on www.regulations.gov for public comment on May 16, 2012. The comment period closed on July 16, 2012. A total of 58 comments were received and have been incorporated into the strategy as appropriate. Also, representatives of several Federal agencies provided comments on the Plan and noted opportunities for future collaboration.

Chapter 1: Detection of Infertility

Public Health Importance

The clinical detection of infertility is important because it can lead to further evaluation and treatment where needed. Similarly, public health surveillance of infertility will be most effective when a standard case definition is established for population-based data collection. No definitive test or case definition currently exists for infertility.[2,3] A range of definitions has been used, and these definitions are often based on a combination of the length of time that the couple has been trying to conceive (or to produce a live birth) and the age of the woman. A clear, standard definition for infertility is needed to ensure timely care for those who need services and to prevent overtreatment for those who may be able to conceive without medical interventions.

To fully understand the negative effects of infertility in the United States and measure progress toward reducing the problem, increased attention is needed to the ongoing collection, analysis, interpretation, and use of population-level data related to infertility. Specifically, researchers need to measure four types of data on a recurring basis: (1) disease incidence and prevalence; (2) prevalence of risk factors for various types of infertility; (3) access to and use, safety, efficacy, and quality of infertility services; and (4) economic and financial aspects of service delivery.

1. **Disease incidence and prevalence.**
   Measurement of disease incidence and prevalence at the population level requires surveillance of infertility, including the type(s) of infertility, and the spectrum of disorders and conditions that directly contribute to the diagnosis—each of which has different implications for detection, prevention, and management.

   Other key indicators to monitor include semen quality, time-to-pregnancy, recurrent pregnancy loss, male and female sterilization (as well as sterilization reversal), and resolved infertility. Researchers also need to estimate and track the size of subpopulations that may need or potentially benefit from fertility preservation. For example, people with cancer, autoimmune disorders, or bleeding or clotting disorders may benefit from fertility preservation methods such as the use of drugs to protect the ovaries during chemotherapy or cryopreservation of ovarian or testis tissue, eggs or sperm, or embryos obtained through *in vitro* fertilization.

2. **Prevalence of risk factors for various types of infertility.**
   Surveillance of possible risk factors for infertility should include data on sociodemographic characteristics (e.g., age, race/ethnicity, education, place of residence, socioeconomic status), health behaviors (e.g., use of alcohol, tobacco, illicit drugs, anabolic steroids), body weight and related factors, adherence to screening and treatment recommendations related to risk factors, physical and mental health conditions (e.g., genetic disorders, sexually transmitted infection (STI), obesity, depression, cancer), environmental exposures (e.g., household chemicals), occupational exposures (e.g., industry type, specific occupations, identified chemical or physical exposures in the workplace), and prenatal and intergenerational exposures (e.g., diethylstilbestrol).
3. **Access to and use, safety, efficacy, and quality of infertility services.**
   Collection of population-based data on access to and use and quality of infertility services requires the identification of key indicators related to screening, diagnosis, laboratory services, state-specific infertility treatment mandates, and psychosocial determinants (e.g., fertility goals). These indicators may influence service-seeking behavior, counseling, and treatment decisions.
4. **Economic and financial aspects of service delivery.**
   Finally, to estimate and track the economic and financial aspects of service delivery, researchers need to collect data in several areas. Examples include the use and cost of infertility services, the cost of infertility treatment, the direct and indirect costs of untreated and treated infertility (regardless of the reproductive outcome), and the cost-effectiveness of alternative treatment strategies. Data are also needed on the economic effect of reducing barriers to diagnosis and treatment and the long-term health care costs of adverse maternal and child outcomes related to infertility treatment.

The Challenge

Clinical Detection and Surveillance

To facilitate comparisons of infertility estimates across clinic and population-based studies, clinical detection and public health surveillance of infertility should be based on standard diagnostic criteria and case definitions for both male and female infertility. Appropriate clinical and behavioral indicators are needed to improve the detection of infertility in the US population. To effectively prevent and manage infertility, the clinical diagnosis must be based on scientific evidence. Public health surveillance of infertility depends on the systematic, recurring collection and management of accurate data. Ideally, surveillance systems that capture infertility data will use standard case definitions that can be applied across multiple data systems and over time. For surveillance to be maximally effective and useful, the data collected must identify types of infertility, including specific infertility diagnoses, and associated risk factors and outcomes.

Several public health surveillance systems include ongoing, population-based surveys that currently collect data on a variety of reproductive behaviors, infertility treatments and services sought, and outcomes. Examples include CDC-directed systems such as the National Vital Statistics System (NVSS), National ART Surveillance System (NASS), Pregnancy Risk Assessment Monitoring System (PRAMS), National Health and Nutrition Examination Survey (NHANES), and the aforementioned NSFG. The current systems, described further at the end of the plan, all have several limitations, such as the lack of uniform case definitions and standardized information across systems. For example, methods for quantifying infertility and impaired fecundity can differ by data source. Information is lacking on many key indicators, such as the prevalence of specific types of infertility for both women and men, the success rates and use of infertility treatments (other than ART) among women and men, and adverse maternal and child health outcomes associated with infertility treatment.

In addition, current surveillance systems do not include measures of all relevant indicators. As a result, these systems do not provide a comprehensive assessment of the magnitude of the incidence, prevalence, risk factors, and outcomes associated with infertility. These systems could improve the quality of data related to infertility by collecting information on the length of time between the start of attempts to conceive and pregnancy or the current duration of time spent having unprotected vaginal intercourse.[41,42] This information could be reported by participants in population-based surveys. Registries of individual cases could also provide information to better assess infertility in the population and the safety and effectiveness of treatment. These registries could

collect information, for example, on egg donors, patients treated with specific classes of fertility drugs, cancer patients who use fertility preservation methods, or military veterans with service-related infertility. Initiatives to achieve prospective follow-up of couples planning or at risk for pregnancy are important for establishing incidence and attributing clinical factors among couples undergoing infertility evaluations.

Scientific and Programmatic Opportunities

The following are specific actions that public sector agencies, professional and consumer organizations, and other partners and stakeholders could take to help improve the detection of infertility in the United States.

1. **Develop and validate standard case definitions for population-based and clinical surveillance of infertility.**

   Development of standard case definitions for infertility and related factors would provide uniform measures for use in public health and clinical practice. These standard definitions could improve the synthesis of information and ultimately lead to improved evidence-based guidelines and recommendations for detecting, preventing, and managing infertility.

2. **Improve the surveillance of infertility and related factors.**

   Population-based surveys could be developed or existing systems could be expanded to support the measuring and monitoring of the prevalence and incidence of infertility, associated risk factors, and health outcomes in women, men, and offspring. For example, the NSFG could better evaluate infertility by increasing participant sample sizes related to the use of infertility treatment, adding new survey questions about experiences with infertility diagnosis or treatment, and extending its surveys to include older women and men who are more likely to have experienced infertility.

   Questions that directly query women and men about infertility could also be added to other large population-based surveys (see *List of Public Health Surveillance Systems and Surveys Referenced*) that currently collect data relevant to understanding health conditions and factors that may affect fertility. Similarly, to improve the value of public health surveillance of ART cycles and outcomes and better understand infertility, additional data from the male partner such as infertility diagnosis and semen quality could be added to the National ART Surveillance System. Further, multiple records in this system could be linked to allow evaluation of the effectiveness and safety of ART by patient instead of by treatment cycle. This enhancement would strengthen the ability to evaluate the short- and long-term effects of ART use on maternal and infant outcomes on a per-patient basis. Finally, the development of new surveillance systems to monitor the use and health outcomes of non-ART treatments for infertility should be explored. Birth certificates include information on ART and non-ART treatment that could also monitor the relationship to adverse pregnancy and birth outcomes. A possible approach for this could be identifying and including structured data elements to collect such information in electronic health records.

Chapter 2: Prevention of Infertility

Public Health Importance

Many questions remain about the prevention of infertility. Although unknown, the proportion of infertility that may be preventable is suspected to be substantial.[39] Established and possible causes of infertility include genetic abnormalities, aging, certain acute and chronic diseases, behavioral risk factors (e.g., body weight, smoking),[43] and exposure to certain environmental, occupational, and infectious agents.

One example of a recognized, preventable risk factor for infertility in women and men is untreated sexually transmitted infection (STI). In particular, infection with *Chlamydia trachomatis* increases the risk of pelvic inflammatory disease (PID) in women.[44-46] If left untreated, PID can cause structural or functional fallopian tube damage known as tubal factor infertility. Tubal factor infertility, which may be caused by *Chlamydia trachomatis* or by other infections, such as *Neisseria gonorrhoeae*, is estimated to affect as many as 18% of women using ART to treat infertility.[39] Among men, *C. trachomatis* infection has been linked with nongonoccocal urethritis, epididymitis, and lower sperm counts.[47] In addition, substantial racial disparities have been identified in the rates of chlamydial infection. For example, the prevalence among non-Hispanic blacks is about five times higher than among non-Hispanic whites.[48] Racial disparities also exist in the rates of chronic conditions that affect fertility, such as fibroids.[49] Public health monitoring of the prevalence of such conditions and associated risk factors can lead to improved identification, guidance, and implementation of effective prevention and management strategies.

The Challenge

Understanding the Causes of Infertility

To be able to develop and implement effective public health interventions, researchers need standard case definitions for male and female infertility and its causes. Although much is understood about the causes of infertility, more research from cohorts that are carefully followed up prospectively would help identify the causes and percentage of infertility cases that can be attributed to specific risk factors and medical conditions. However, research on infertility is inherently complicated because infertility is generally diagnosed only when a man, woman, or couple attempts to become pregnant. People who are not actively trying to conceive will typically not have the opportunity to be evaluated or receive a diagnosis of infertility. Current surveillance systems are not designed to identify the spectrum of women and men who may have unrecognized infertility.[50]

New methods for measuring infertility and for identifying and improving conditions that are precursors to infertility are needed. Improving our understanding about the causes of infertility will enhance preventive and therapeutic options for both women and men and reduce our reliance on the use of more invasive methods to treat infertility at later stages.

Research is needed to better understand many known and potential causes of infertility, including but not limited to the following:

- Reproductive aging—that is, establishing biomarkers, determining the predictors and correlates of early depletion of the ovarian reserve, and the effects of age on semen quality and reproductive function.
- Important developmental periods—that is, identifying factors that affect fertility during certain developmental periods (e.g., preconception, *in utero*, puberty, transgeneration) to identify the best time for intervention.
- Infectious diseases—that is, the proportion of cases of tubal factor infertility attributable to infectious diseases and the role of specific infections, such as chlamydia, gonorrhea, mycoplasmas, trichomoniasis, bacterial vaginosis, tuberculosis of the reproductive tract, microbial organisms associated with reproductive tract infections, epididymoorchitis, prostatitis, and mumps.
- Chronic conditions and diseases—including endocrine and metabolic diseases such as primary ovarian insufficiency, polycystic ovary syndrome, hypothalamic amenorrhea, menstrual cycle defects, endometriosis, uterine leiomyomata, thyroid disorders, metabolic syndrome, diabetes, autoimmune disorders, meiotic aneuploidy, cystic fibrosis, varicocele, testicular disorders, multiple sclerosis, general urologic health, and immune-mediated disorders.
- Behavioral factors—such as diet, exercise, sleep, psychological and physiological stress, caffeine consumption, tobacco and alcohol use, weight gain or loss, nutritional disorders, illicit or prescription drug use, and illicit use of anabolic steroids and growth hormones.
- Iatrogenic causes—such as chemotherapy or associated medications for testicular or ovarian cancer and antiretroviral therapy for HIV/AIDS.
- Occupational and environmental hazards—such as radiation, repetitive motion or posture, injury (e.g., reproductive or urinary tract trauma such as that experienced during military duty), or natural or synthetic chemicals and compounds with hormonal activities (e.g., endocrine disruptors).
- Genetic influences—such as male karyotype abnormalities, Y chromosome microdeletions, or androgen receptor gene abnormalities.

Public Health Interventions for Prevention

Public health interventions to prevent infertility must be based on evidence from research. This translation of science into public health practice requires the development of systems and policies to incorporate research results into prevention programs. The prevention of infertility should be integrated into a broader agenda for reproductive health promotion for both women and men. Programs, interventions, strategies, and other methods for preventing infertility must be developed and evaluated. Examples of these activities include but are not limited to the following:

- Comprehensive approaches to STI screening, treatment, prevention, and education to reduce infertility and to address economic and racial disparities in access to STI prevention, testing, and treatment, use of infertility services, and outcomes of treatment.[51,52]
- Interventions to reconcile and clarify simultaneous public health messages for preventing infertility and for preventing unintended pregnancy among youth.
- Chronic disease prevention and health promotion programs to reduce the incidence and severity of conditions such as diabetes, polycystic ovary syndrome, and infertility related to polycystic ovary syndrome.

- Methods to measure reproductive potential (including markers of ovarian reserve and semen analyses) and preserve fertility before, during, or after medical therapies that could lead to iatrogenic infertility.
- Measures to protect the reproductive health and fertility potential of workers who may be exposed to environmental and occupational hazards by translating research findings, technologies, and information into evidence-based practice.
- Methods to accurately assess environmental and occupational exposures, such as laboratory biomonitoring, control technologies, screening tools, and interventions.
- Programs aimed at behavioral factors that may affect infertility, such as programs to prevent use of illicit drugs, tobacco, and anabolic steroids; improve nutrition; and promote adequate levels of physical activity.
- Research to determine the cost effectiveness and cost benefit of programs aimed at preventing infertility.

Scientific and Programmatic Opportunities

The following are specific actions that public sector agencies, professional and consumer organizations, and other partners and stakeholders could take to help prevent infertility in the United States.

1. **Expand knowledge about infertility prevention through collaborative efforts to identify, prioritize, and address research gaps.**

   Conducting more research on ways to prevent infertility requires collaboration from a range of disciplines, including basic science, epidemiology, genomics, and the clinical, behavioral, and social sciences. Governmental and nongovernmental organizations must work together to address the gaps in our understanding of the causes of both female and male infertility and to increase opportunities for prevention. These efforts should focus on several factors, including the effects of age, behavioral risk factors, chronic conditions and diseases and their treatment, genetic disorders, and exposure to environmental, occupational, and infectious agents.

2. **Expand laboratory capacity and services to help address knowledge gaps about environmental, occupational, and infectious causes of infertility.**

   Improvements in laboratory-based infertility research would improve our understanding of how environmental, occupational, and infectious exposures might adversely affect fertility. For example, public health laboratories must be able to conduct biomonitoring of chemicals or their metabolites in human specimens (e.g., blood, urine, hair).

3. **Increase awareness of the prevalence and known causes of infertility.**

   Scientific knowledge should be rapidly shared and translated into public health programs and evidence-based practices. Educational programs should be developed and conducted to expand awareness among youth and adults about the prevalence and known causes of infertility. These programs should be integrated with other activities designed to promote reproductive health, and they should take into account the culture and age of their audience.

4. **Develop and promote behavioral and clinical approaches to preventing infertility based on the best scientific evidence available.**

   Efforts should focus on the design, evaluation, and implementation of programs, interventions, strategies, clinical services, and other methods that can effectively address the known causes of infertility (e.g., behaviors that increase the risk of infertility).

5. **Support and improve access to quality services, including screening, diagnosis, and treatment services for known causes of infertility.**

   Further integration of infertility services into primary care settings would help expand access to screening, testing, and counseling. In particular, economic and racial disparities in access to and use of infertility services and treatment outcomes could be reduced by expanding services at public health and other clinics that target underserved populations. To improve the quality of these services, public health providers may need more training.

Chapter 3: Management of Infertility

Public Health Importance

According to the 2006–2010 NSFG, 12% of women in the United States aged 15–44 years, or their husbands or partners, have ever used one or more infertility services.[27] This percentage likely underestimates the true burden of infertility because it excludes women and men who have not yet sought services. Although most infertility services do not involve ART,[32] the prevalence of ART use has been increasing. The number of ART cycles (which are primarily *in vitro* fertilization [IVF] cycles) performed in the United States increased from 99,629 in 2000 to 163,039 in 2011, and ART procedures were used for more than 1% of total births in the United States in 2011.[18]

Fertility treatments can pose health risks for women, men, and their children. For example, the use of drugs to induce ovulation can lead to ovarian hyperstimulation syndrome (OHSS), which is characterized by ovarian enlargement and which, in serious cases, can cause morbidity and be life-threatening. Infertility treatments, including both ART and non-ART procedures in which medications are used to stimulate ovulation, are associated with an increased risk of multiple-order births, which carry health risks for women and infants and increased costs.[33]

Infertility treatment can also be expensive, and disparities exist in access to and use of these services. The average cost of a single cycle of IVF in the United States has been estimated at more than $12,000.[39] Fifteen states had laws requiring insurers to cover or offer coverage for some level of infertility treatment in 2006.[53] Insurance coverage could increase the use of elective single embryo transfer in ART procedures, thereby improving birth outcomes from these procedures.[53] Economic, regional, and racial/ethnic disparities in access to and use of infertility services are clearly present.[51-54] Even in states with more equitable access to care because of insurance mandates, racial/ethnic differences have been found in the rate of adverse health outcomes after infertility treatments.[51]

More research is needed to improve the management of infertility. This research could:

- Identify new approaches for safe and effective diagnosis and treatment of infertility in women and men that could reduce the need for ART or other medical approaches to achieve pregnancy.
- Identify and reduce exposure to treatment regimens that pose increased risk of adverse outcomes.

- Address the ethical and social issues related to certain clinical procedures, as well as the financial costs of medically assisted reproduction.
- Eliminate disparities in access to safe and effective treatment for infertility.

The Challenge

New treatments for infertility that are safer and more effective than current treatments need to be developed, and more research is needed to improve the safety and efficacy of currently available treatments. Examples of current infertility treatments that could be further improved include the following: regimens to induce ovulation, adjuvant therapy to enhance the success rates of IVF, regimens to prevent or treat OHSS, methods to preserve the integrity of oocytes and embryos, treatments to prevent recurrent pregnancy loss, treatments to modify male factors, and, continual efforts to promote overall health across the lifespan. Other areas that could be addressed include finding ways to lower the cost of ART treatment, developing treatments that are noninvasive or minimally invasive and encouraging their use, and improving infertility management education for health care providers.

Given the increased risks to the health of mothers and infants that are associated with multiple births, treatments that do not increase the chances of this outcome are needed. The safety and efficacy of the use of donors for infertility management (e.g., oocyte donation, oocyte cryopreservation, sperm donation, reproductive tissue donation, gestational surrogacy) should be evaluated for donors, recipients, and children conceived.[55] In addition, the long-term effects of infertility treatments on adults—as well as on children conceived as a result of the treatment—need to be more fully assessed.

More research is needed to improve communications with diverse populations of women and men experiencing infertility. Psychological and behavioral research could help improve our understanding of issues related to the effect of infertility on their emotional well-being and quality of life and the use of services for dealing with infertility, medical and other service-seeking behaviors by individuals and couples experiencing infertility, decision-making around the issue of infertility and approaches for single adults and couples trying to have children, and the effect of multiple gestation and adverse pregnancy outcomes on parents and children.

Efforts are needed to identify the best methods for providing equitable access to infertility services among those in need while minimizing adverse and costly health outcomes, such as those associated with multiple births.

Studies should examine the cost-effectiveness of different treatment methods for women and men (e.g., pharmaceutical management versus microsurgical treatment of male or female factors, single embryo transfer versus higher-order embryo transfer), including the costs of patient outcomes (e.g., multiple births). These investigations could use administrative (e.g., insurance) data and data from other sources. For example, if researchers can ensure adequate protection of the security and confidentiality of the data, studies could use insurance and hospitalization datasets to monitor the costs related to treating infertility, including hospitalization costs, out-of-pocket expenses, and days of work lost.

Infertility prevention and management practices could potentially be improved by engaging public and private payers for those services, conducting cost-effectiveness analyses, developing guidelines and recommendations for providers of infertility services, and improving educational information about infertility for the public. Guidelines should be based on scientific evidence of the safety and effectiveness of infertility services and treatments, and they should take into account multiple considerations. For example, some infertility services, such as gestational surrogacy and egg or sperm donation, raise complex ethical, legal, and social questions—including questions about coercion, payment for surrogates or donors, and ability to follow up with donors to assess possible long-term effects on their mental and physical health. Guidelines might also include counseling on alternatives for achieving parenthood (e.g., adoption) or choosing to live without children. The appropriate use of infertility treatment advances that allow extension of the age at which conception, carrying a pregnancy

to term, and delivery may now be achieved must be balanced against another—public health and societal interests in preventing adverse health outcomes and excessive health care costs.

Scientific and Programmatic Opportunities

The following are specific actions that public sector agencies, professional and consumer organizations, and other partners and stakeholders could take to help manage infertility in the United States.

1. **Monitor and evaluate the short- and long-term safety of infertility interventions.**

   Research and enhanced surveillance should focus on the safety, efficacy, and use of different infertility services and treatments for managing male and female infertility in different populations. These efforts would improve our understanding of the possible short-term effects of infertility treatment. They would also improve our understanding of the possible long-term effects of infertility treatment on women and men (regardless of the success of the treatment) and on any children conceived as a result of these treatments.

2. **Eliminate disparities in access to high-quality infertility services, including diagnosis, referral, and treatment.**

   Efforts should focus on reducing disparities in access to, use of, and outcomes related to infertility services. Integration of infertility services into primary care settings that target underserved populations could help reduce the economic and racial disparities in access to infertility treatment.

3. **Promote further development, adoption, evaluation, and implementation of evidence-based guidelines and recommendations that address the prevention, diagnosis, and management of infertility.**

   Evidence-based guidelines and recommendations for providing infertility services to women and men from professional medical associations (such as the American Society for Reproductive Medicine and the American Urological Association) should be evaluated on their use and effectiveness, and new guidelines should be developed as needed. Guidelines and recommendations should be based on scientific evidence. They should also be comprehensive enough to address the numerous—and often complex—issues that surround the management of infertility. These issues include complications associated with infertility treatment (e.g., higher-order multiple births, OHSS), and bioethical and cost considerations.

4. **Develop educational programs to increase awareness of the safety and effectiveness of treatments for infertility and other options for managing infertility.**

   Efforts should be made to ensure that health professionals have adequate resources and training to educate patients and the public about the benefits and risks of the infertility services available as well as other options for dealing with infertility (e.g., adoption).

Conclusion

This National Action Plan identifies many opportunities for reducing infertility and its causes in the United States. It highlights scientific and programmatic opportunities to strengthen the public health approach to detecting, preventing, and managing various types of infertility. Governmental and nongovernmental organizations must work together to address the gaps in our understanding of the causes of both female and male infertility and to increase opportunities for prevention. Important partners in these efforts should include Federal, state, and local agencies; the scientific community; health care professionals; insurance providers; employers; industry; nonprofit organizations; and organizations representing people coping with infertility. This discussion is critical to the call for action by the White Paper: *"… a coordinated and multidisciplinary approach to address infertility, from primary prevention to treatment and support."* [39]

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List of Public Health Surveillance Systems and Surveys Referenced

National ART Surveillance System

www.cdc.gov/art/NASS.htm

In collaboration with the Society for Assisted Reproductive Technology, CDC supports the National ART Surveillance System (NASS), a Web-based system for reporting data on assisted reproductive technology (ART). This surveillance system captures more than 95% of the estimated ART procedures performed annually in the United States. The system collects data on each client's medical history (such as infertility diagnoses), clinical data on the ART procedure, and data on resulting pregnancies and births. Data from NASS are used to prepare CDC's Annual Report on ART Clinic Success Rates.

National Health and Nutrition Examination Survey

www.cdc.gov/nchs/nhanes.htm

CDC began the National Health and Nutrition Examination Survey (NHANES) program as a series of surveys focusing on different population groups or health topics in the early 1960s. The surveys became a continuous program in 1999. NHANES uses household and private interview methods to collect annual health and nutrition information on a nationally representative sample of noninstitutionalized civilians. Health interview topics include the following: current health status, medical conditions, reproductive health (pregnancy history, lactation, use of contraception, and men's and women's health conditions), health insurance coverage, use of health care services, lifestyle behaviors (including sexual, illicit drug, alcohol, and tobacco use behaviors), occupational history, and environmental exposure to chemicals.

National Survey of Family Growth

www.cdc.gov/nchs/NSFG.htm

CDC conducts the National Survery of Family Growth (NSFG) to collect national estimates of the prevalence of infertility and impaired fecundity and the use of infertility services in the United States among males and females. The survey gathers information on family life, marriage and divorce, pregnancy, infertility, use of contraception, and men's and women's health. Survey results are used to plan health services and health education programs and to conduct statistical studies of families, fertility, and health. Recently added questions to the survey help researchers investigate the associations between cancer history and various factors, including the use of infertility services, as well as use of chlamydia screening to assess adherence to current CDC screening recommendations.

National Vital Statistics System

www.cdc.gov/nchs/births.htm

CDC cooperates with the states to maintain the National Vital Statistics System (NVSS), a Federal compilation of births and other vital statistics data. Birth certificates contain maternal and paternal information (e.g., education, race, age) and information on the infant (e.g., birth date, plurality, sex, birth weight, congenital anomalies, complications of labor and delivery). Because the 2003 revision of the standard US birth certificate added information about the use of infertility treatment, birth certificates could become an important source of information on the association between these treatments and maternal and child health.

Pregnancy Risk Assessment Monitoring System

www.cdc.gov/prams

The Pregnancy Risk Assessment Monitoring System (PRAMS) is a joint project of CDC and state health departments. It uses surveys to collect state-specific, population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy. The goal of the system is to improve the health of mothers and infants by reducing adverse outcomes, such as low birth weight, infant death and disease, and maternal disease. Selected states collect data on the use of infertility treatment. These data may provide useful information on the association between infertility and infertility treatments and adverse health outcomes for mothers and infants.

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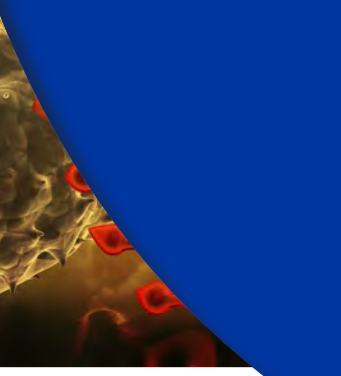

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