OUTLINE FOR A NATIONAL ACTION PLAN FOR THE PREVENTION, DETECTION AND MANAGEMENT OF INFERTILITY

May 7, 2010

TABLE OF CONTENTS

I. BACKGROUND

Infertility as a priority for public health

Infertility is an emerging public health priority. In 2002, the National Survey of Family Growth (NSFG) found that two million couples in the United States were infertile (i.e., had not conceived during the previous 12 months despite trying) (1) An estimated 7.3 million, or 12% of American women aged 15-44 years had received infertility services (including counseling and diagnosis) in their lifetime. More than 1.1 million women sought medical help to get pregnant in the previous year (1). Although the focus of research and services has traditionally been on women, fertility impairments may be just as common among men (2). A total of 7.5% of all sexually experienced men reported a visit for help with having a child; 2.2% reported a visit in the past year, equivalent to 3.3-4.7 million men reporting a lifetime visit and 787,000-1.5 million reporting a visit during the previous year (3). Recent trends toward postponing age at first pregnancy have highlighted the natural limits of fertility and accelerated the development and use of medical technology such as Assisted Reproductive Technology (ART) to overcome such limits (4). The proportion of first births to women aged 30 years and older has increased more than fourfold since 1975, from 5% to 24% in 2006. The absolute number of these births increased from more than 69,000 to approximately 405,000 during this period (5, 6). Although some perceive infertility as a quality-of- life issue, the American Society for Reproductive Medicine (ASRM) regards infertility as a disease (7). Similar definitions are being considered by the European Society of Human Reproduction and Embryology (ESHRE), and by the International Committee Monitoring Assisted Reproductive Technologies (ICMART). A U.S. Supreme Court opinion agreed with a lower court statement that reproduction is a major life activity and confirmed that conditions that interfere with reproduction should be regarded as disabilities, as defined in the Americans with Disabilities Act (8).

Possibilities for prevention

Known or potential causes of infertility include genetic abnormalities, environmental, occupational, and infectious agents, certain diseases, delayed childbearing, and behavioral risk factors. We do not know what proportion of the infertility burden can be prevented, but it may be substantial (4). For example, tubal infertility affects 18% of the couples who try to overcome infertility using assisted reproductive technology (ART) (9) and is typically the consequence of chronic pelvic inflammatory disease (PID), which can lead to tubal scarring. Clinical trials have shown that the risk of PID can be greatly decreased by early detection and treatment of sexually transmitted diseases (STDs) and, in particular, chlamydia infection (10). More than 1 million chlamydia cases are reported to the Centers for Disease Control and Prevention (CDC) annually (11). In 2006, reported chlamydia rates were eight times higher among African Americans than among whites, highlighting the large racial disparities in this important risk factor for infertility (11). In a representative sample of the US population participating in the

National Health and Nutrition Examination Survey (NHANES), the prevalence of chlamydia infection was 2.2%. Among women, the highest prevalence of chlamydia was in those 14 to 19 years old, whereas among men it was highest in those 14 to 29 years old. Among women with a history of gonorrhea or chlamydia in the previous 12 months, chlamydia prevalence was 16.7% (12). Despite continuous promotion efforts, the uptake of chlamydia screening is still relatively low (13). While the causal role of STDs on tubal infertility is well established and randomized trials have documented that chlamydia screening prevents PID, the impact of chlamydia screening programs on the prevalence of infertility is unclear (4).

Environmental and occupational hazards account for an unknown proportion of infertility, but are suspected causes of declining human sperm quality in industrialized countries (14). Environmental exposure to chemicals that may interfere with fertility is common. For example, bisphenol A (BPA) is a chemical employed in the manufacture of polycarbonated plastics that has been the subject of recent debate. BPA is a weak estrogen, and animal studies suggest that it interferes with the development of reproductive organs and with the production of sex hormones: the effect of low BPA doses on human reproduction is unknown (15). The NHANES 2003-2004 laboratory results provided the first nationally representative data for urinary BPA. BPA was measured in persons 6 years of age and older, and was detected in 92.6% of persons tested. The concentrations of BPA differed by race and ethnicity, age, sex, and household income (15, 16). It has been proposed that in women, gene-environment interactions are likely to be involved in causing premature ovarian insufficiency (POI), endometriosis, and uterine fibroids (17). A recent meeting focusing on the effect of environmental contaminants on infertility and associated reproductive health conditions highlighted the evidence that very low doses of some biologically active contaminants can alter gene expression important to reproductive function; that exposure during fetal development can have long-term adverse effects, including reproductive health effects; that multiple exposures can act synergistically; and that people differ in susceptibility to exposures. The consensus statement emphasized the paucity of adequate epidemiologic studies of the reproductive health effects of environmental exposures (17). These remarks are also relevant to occupational reproductive health research. Many occupational reproductive toxicants are still in regular commercial or therapeutic use, and many more workplace substances are suspected of producing reproductive toxicity but have not been studied adequately. The National Occupational Research Agenda gives high priority to the development of new methods for identifying reproductive hazards in the workplace and prioritizes 43 chemicals for field studies among potentially exposed workers (18). There is increasing evidence that lifestyle factors such as tobacco smoking and obesity, which can cause chronic disease and disability later in life, can also adversely affect fertility during the reproductive years (19, 20). The metabolic disorder associated with the polycystic ovary syndrome (PCOS) has highlighted the link between overeating, obesity, insulin resistance, and the endocrine changes that reduce fertility in women with PCOS (20). NHANES 2005-2006 data revealed that over 34% of adults aged 20 years and older are obese (21). Fertility impairments resulting from the treatment of diseases such as cancer (22-24) and infection with human immunodeficiency virus (HIV) (25, 26) may also be successfully

addressed. Available ART procedures may offer the possibility of maintaining the ability to procreate among individuals who cope with life-threatening diseases and may experience infertility as a side effect of treatment.

Need for better access to diagnosis and treatment

Social and racial disparities in health status and in the frequency of certain risk factors (e.g., STDS that may lead to infertility if untreated) suggest that preventable causes of infertility disproportionately affect the less privileged. In a recent study, among non-surgically sterile women, African American women had a two-fold increase in the odds of reporting a history of infertility (27). Financial barriers limit access to diagnosis, evaluation and treatment, and may lead to selectively underestimating the frequency of infertility in the same population groups. (28) Thus, it is difficult to interpret the available data. On the other hand, delaying childbearing may be more common among professionals and other higher-income groups, making these groups more vulnerable to the cumulative effect of causes of infertility, including the effect of aging. Different subgroups may have infertility of different etiology. According to the NSFG, only about 50% of the women who were infertile in 2002 reported seeking medical advice or testing, and even fewer received any form of treatment (1). One barrier to treatment is lack of insurance coverage: in many states, the couple is directly responsible for paying for the initial infertility assessment and subsequent treatment (4). In addition, economic, racial and ethnic disparities may be present not only in the frequency of fertility impairment or access to treatment but also in treatment outcomes (29). In the United States the number of ART procedures was about 500 per million population in 2006 (9), whereas in Europe during the same year the number ranged from 400 (Montenegro) to 2300 (Denmark) (30).

Preventing adverse outcomes of infertility treatment

ART has been used in the United States since 1981 to help women become pregnant, most commonly through IVF of human eggs followed by transfer of the embryos into the woman's uterus (9). Use of ART in the United States has doubled over the past decade, and ART-born infants now account for more than 1% of all U.S.-born infants and 18% of all multiple births (31). The proportion of infants born after ART is larger in states where statutes mandate insurance coverage of infertility treatment (32). Although infertility treatment, including ART, is generally safe, adverse outcomes have been described both in women undergoing ART and in infants born from these procedures (33). Ovarian hyperstimulation syndrome is a rare but very serious adverse effect of ART and ovarian stimulation (34). Multiple-gestation pregnancies are much more common after infertility treatment than after natural conception and increase the risk for maternal complications (35, 36). Multiple-birth infants are at increased risk for low birth weight, preterm delivery, infant death, and disability among survivors (35–40). Recent systematic reviews of the literature (41, 42) indicate that ART-conceived singletons also face increased risks for low birth weight, very low birth weight, preterm delivery, and fetal growth restriction. These findings have been confirmed in population-based studies in the United States (43, 44). For infertile women who have a good prognostic profile (i.e., a high expected

probability of success with ART, as indicated by age under 35 years, no history of failure with ART, and the production of multiple embryos of good quality), the simplest and most effective strategy for reducing the risk of adverse ART outcomes is elective single embryo transfer (SET) (4).

Process for developing the National Action Plan outline

CDC, as the leading public health agency of the federal government, has long been concerned with infertility, its causes and prevention. CDC conducts:

- Surveillance to monitor the prevalence of infertility and the use, efficacy and safety of infertility services and treatment;
- Research on the infectious, environmental and occupational causes of infertility, on the links between the treatment of chronic diseases and infertility, and on the links between infertility treatment and birth defects, developmental disabilities and other birth outcomes;
- Public health programs for the primary and secondary prevention of infertility, especially in the area of STDs and reproductive tract infections.

In 2007, an agency-wide ad hoc working group formed to coordinate infertility activities at CDC and found that considerable gaps and opportunities remain in public health surveillance, research, communications, programs and policy development. This assessment led to the publication of a white paper by the group in 2008, in order to highlight infertility prevention, detection and management (4). In addition, the group hosted a Symposium on Infertility as a Public Health Issue at CDC in Atlanta, GA on September 14-15, 2008. Stakeholders from federal agencies, professional and consumer organizations, academia, the health care community and industry were invited to review infertility causes, consequences and potential interventions. The key questions posed during the symposium were:

1) On the basis of what we already know, what can be done now?
2) What are the most important gaps in our knowledge where we need to put resources into gathering new information?
3) What organizations could best address the advancement of these issues?
4) Can your organization play a role in the advancement of these issues?

Participants requested that the CDC Working Group outline a national action plan on infertility based on material presented, and group discussions, at the Symposium. A preliminary draft was reviewed by a group of experts who had attended the Symposium and by the CDC Infertility Working Group. The present outline includes information presented and discussed at the Symposium, as well as follow-up conversations and correspondence, and includes areas that participants, stakeholders, and/or workgroup members thought important to consider for a NAP on infertility. The outline has been circulated to a broad coalition of stakeholders to facilitate the discussion of priorities and future development of a detailed plan. The present version incorporates changes made to accommodate stakeholder comments received on or before November 30, 2009.

Whereas CDC staff compiled this document, it is important to clarify that the Outline does not necessarily represent the agency's official view or policy, nor the view or policy of any other organization. We hope that with the guidance provided by a national action plan, the efforts of the stakeholders within and outside government will be better focused and coordinated, and will be more effective in decreasing the burden placed by infertility on the public's health.

II. GOALS OF THE NATIONAL ACTION PLAN

The overarching goal of the Plan is to promote, preserve and restore the ability of people who live in the United States (US) to conceive and the ability of women in the US to carry a pregnancy to term and deliver a healthy child. The specific objectives of this plan are:

1) To reduce the burden of infertility and impaired fecundity in the United States by promoting behaviors that maintain fertility, by promoting prevention, early detection, and treatment of infections (such as chlamydia) and other medical conditions that lead to infertility, and by removing or reducing environmental and occupational threats to fertility;

2) To improve access to the diagnosis and treatment of infertility and eliminate disparities in infertility care;

3) To improve the efficacy and safety of infertility treatment; and

4) To improve the quality of life of people who live with infertility in the US.

To achieve the goals listed above, the recommendations in this plan are grouped into five categories:

1. Evaluating Impact: Monitoring the Burden and Measuring Progress;
2. Advancing the Knowledge Base: Primary, Secondary and Tertiary Prevention Research;
3. Advancing Policy: Defining the Issues and Finding the Needed Solutions;
4. Strengthening Capacity: Transforming the Organization and Structure of Public Health Agencies and Partnerships; and
5. Taking Action: Putting Present Knowledge to Work

The Institute of Medicine has defined three core functions of public health: assessment, policy development and assurance (45). This model provides the foundation for grouping actions into the five categories described above. Assessment is regular and systematic collection, assembly, analysis and availability of information on the health of the community. Policy development is promoting the use of the scientific knowledge base in decision-making about comprehensive public health policies which serve the public interest. Assurance is providing services to constituents necessary to achieve agreed upon goals by encouraging actions by other entities (private or public sector), by requiring such action through regulation, or by providing services directly. The public health concepts of primary, secondary and tertiary prevention also are employed to categorize actions. Primary prevention focuses on the prevention of diseases and

conditions before their biological onset (46). Secondary prevention involves the identification and interdiction of diseases that are present in the body, but that have not progressed to the point of causing signs, symptoms, and dysfunction. These preclinical conditions are most often detected by disease screening (and follow-up of the findings) (47).Tertiary prevention consists of the prevention of disease progression and attendant suffering after it is clinically obvious and a diagnosis has been established. This activity also includes the rehabilitation of disabling conditions (48).

III. EVALUATING IMPACT: MONITORING THE BURDEN AND MEASURING PROGRESS

In order to fully understand the impact of infertility on public health in the US, as well as to measure progress towards our objectives of reducing the burden of infertility, there are key data elements that are needed as well as areas that need further attention. These are listed below. Current surveillance systems (section IX, Appendix A) address certain important aspects of infertility, but are deficient in multiple areas and need to be expanded and strengthened. CDC, as the leading federal public health agency, should consider enhancing surveillance by including the necessary data elements in existing or new data collection systems. This activity will include identifying current systems and their gaps, as well as developing new data sources as needed and performance measures. The following are selected issues related to conducting infertility surveillance and measures identified in the "white paper" (4) and at the National Symposium on Infertility. These elements need to be reviewed and prioritized for inclusion in a comprehensive infertility surveillance plan.

A. Surveillance Systems and Methods (see section IX, Appendix A)

1. Review, update and integrate existing surveillance systems, develop new systems as necessary
    a. Population-based surveys (e.g., National Survey of Family Growth (NSFG))
    b. Registries (e.g., egg donors, patients treated with specific classes of fertility drugs, cancer patients who use fertility preservation methods)

B. Surveillance targets

1. Measure disease incidence and prevalence
    a. Review definitions and measures of infertility and subfecundity
    b. Address conditions directly leading to infertility (e.g., tubal factor, ovulation disorders, endometriosis, premature ovarian insufficiency (POI), male factor infertility)
    c. Address secondary infertility due to sterilization, subsequent regret and reversal
    d. Address recurrent pregnancy loss
    e. Address sub-populations that may need or potentially benefit from fertility preservation (e.g., cancer patients, patients with autoimmune disorders, patients with bleeding/clotting disorders)
2. Measure prevalence and impact of risk factors
    a. Sociodemographic factors (e.g., age, race, education, place of residence, socioeconomic status (SES))
    b. Behaviors (e.g., tobacco smoking, overweight/obesity, adherence to screening and treatment recommendations)

c. Medical conditions (e.g., genetic disorders, STDs, obesity, cancer)
d. Environmental exposures
e. Occupational exposures (e.g., type of industry, specific occupations, as well as identified chemicals or physical exposures in the workplace).

3. Measure access, utilization, and performance of services
    a. Screening
    b. Diagnosis
    c. Laboratory services (e.g., performance of hormonal measurements, semen quality assessment)
        i. Improve hormonal measurements through standardization
        ii. Conduct population surveys to determine reference ranges for key indicators of endocrine function
    d. Psychosocial determinants (e.g., fertility goals) as modifiers of service-seeking behavior
    e. Counseling
    f. Treatment
        i. Type (ART/non-ART)
        ii. Characteristics of patients who use treatment services
        iii. Barriers to access (e.g., cost, time to service)
        iv. Outcomes
        v. Adverse effects (e.g., pregnancy and perinatal outcomes, and long-term health outcomes of women and men undergoing fertility therapy and of children born after infertility treatment)
        vi. Efficacy and safety of egg and embryo donation (e.g., establish registries or follow up studies to assess health consequences of repeated egg donation by healthy volunteers)
        vii. CDC and FDA should consider collaborating on the surveillance of adverse effects of infertility treatment.
4. Measure economic and financial aspects of service performance
    a. Services utilization and cost
    b. Cost and cost-effectiveness of alternative strategies to family building (adoption)
    c. Economic value of successful infertility treatment
    d. Direct and indirect costs of untreated infertility: quality of life issues
    e. Cost-effectiveness of alternative treatment strategies
    f. Economic impact of reducing barriers to diagnosis and treatment
    g. Long term health care costs of adverse maternal and child outcomes of infertility treatment

IV. ADVANCING THE KNOWLEDGE BASE: PRIMARY, SECONDARY AND TERTIARY PREVENTION RESEARCH

There are substantial gaps in our current knowledge that must be filled in order to improve public health programs addressing infertility. Recommendations based on scientific knowledge need to be incorporated in the strategic research plans of

governmental agencies and nongovernmental organizations. The research agenda needed to develop such recommendations must include a blend of basic science, clinical and epidemiologic investigations, and ethnographic, behavioral and social science studies. The National Institutes of Health (NIH), CDC, American Society for Reproductive Medicine (ASRM) and other professional organizations, academia and consumer advocacy groups should take responsibility for advancing the knowledge base through collaborative research efforts. By combining resources, gaps in knowledge related to infertility may be filled more efficiently and thoroughly to more quickly improve disease prevention and community health as well as patient care and treatment outcomes. Listed below are areas that were identified as needing further research.

A. Advancing measurement methods

1. Develop research to improve definition and measurement of fertility and fecundity (e.g., longitudinal studies of fertile windows, time to pregnancy and spontaneous pregnancy loss)
2. Conduct studies of the correlation between longitudinal assessment of time to pregnancy and retrospective assessment of infertility and subfecundity
3. Develop methods for assessing fertility potential that are not dependent on attempts to conceive

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B. Research needed for primary prevention

1. Improve understanding of the etiology of infertility: determine the proportion of infertility cases that are attributable to specific risk factors (e.g., occupational exposures, STDs) and medical conditions (e.g., obesity, tubal disease, polycystic ovary syndrome).
    a. Coordinate analyses of the National Survey of Family Growth (NSFG), which describes women and men (starting in 2002) who seek infertility care services, and analyses of data bases such at the National ART Surveillance System and national administrative (insurance claims) databases, which describe the infertility diagnoses for women who receive infertility care services and the outcomes of those services.
2. Study the impact of aging on infertility
    a. Assess the impact of maternal and paternal age on infertility and recurrent pregnancy loss
    b. Determine the predictors and correlates of age at menarche that might also predict early depletion of the ovarian reserve
3. Investigate the psychosocial correlates of fertility and family growth
    a. Assess variations in family structure and implications for childbearing and family growth
    b. Assess the sociodemographic and behavioral determinants of advanced age at first attempt to conceive
    c. Assess the determinants of individual and couple fertility goals

d. Assess the attitudes and behaviors associated with childlessness

4. Study the impact of infectious disease
    a. Determine what proportion of tubal infertility is attributable to STD and other infections
        i. Examine epidemiologic study design issues
            1. Case-control studies
            2. Cohort studies(e.g., using the Uppsala Women's Cohort Study (49) as a model for studies to determine risk of infertility from STDs in the United States)
        ii. Determine the impact of STD screening programs on tubal infertility
    b. Investigate specific infections and mechanisms
        i. Established: chlamydia, gonorrhea
        ii. Possible: mycoplasmas, trichomonas, other?
        iii. Pathogenesis of PID, markers of subclinical disease
        iv. Bacterial vaginosis
        v. Tuberculosis of the reproductive tract (association with recent immigration and HIV)
        vi. Metagenomic approach to reproductive tract infections
    c. Develop and evaluate STD screening methods and strategies
        i. Developing and improving point-of-cure rapid screening assays
5. Study the relation between infertility and chronic disease
    a. Endocrine and metabolic diseases
        i. Premature Ovarian Insufficiency (POI)/premature menopause
            1. Develop biomarkers and study risk factors
        ii. Polycystic Ovarian Syndrome (PCOS)
            1. Review definition
            2. Assess heterogeneity of pathophysiological mechanisms
            3. Improve diagnostic criteria and early detection tools
            4. Study the spectrum of conditions that do not meet strict diagnostic criteria (e.g., Polycystic Ovaries (PCO))
            5. Examine interaction with obesity and the metabolic syndrome
            6. Evaluate the impact of chronic disease prevention/health promotion programs on the incidence and severity of PCOS and PCOS-related infertility
        iii. Hypothalamic amenorrhea
            1. Examine possible insults that cause disruptions to hypothalamic GnRH pulse generator
            2. Examine possible abnormalities due to disruptions of the hypothalamic GnRH pulse generator
        iv. Menstrual cycle defects
        v. Endometriosis
        vi. Uterine fibroids
        vii. Thyroid disorders
        viii. Weight gain/loss

1. Estimate the amount of weight gain/loss needed before fertility is affected

ix. Metabolic syndrome and infertility
1. Determine the role of obesity
2. Determine the role of Insulin resistance

x. Early detection/treatment of medical conditions leading to infertility
1. POI
2. PCOS
3. PID

b. Cancer: Improve knowledge about the possible link between cancer and infertility, and improve the prospect of fertility preservation by gathering better infertility and pregnancy rate data from well-defined cancer populations.
i. Evaluate specific cancers associated with infertility
1. Testicular
2. Ovarian

c. Evaluate other diseases/disorders associated with infertility (e.g., autoimmune disorders, meiotic aneuploidy, multiple sclerosis)

6. Evaluate medical treatment as a cause of infertility
a. Identify diseases whose management may interfere with fertility (cancer, HIV infection/AIDS, etc.)
b. Assess the impact of specific treatment modalities (e.g., chemotherapy, radiation, hormonal) and their timing on fertility
c. Develop methods to measure reproductive potential before and after treatment
i. Ovarian reserve markers are needed
d. Develop strategies to prevent infertility before or during therapy
e. Assess potential interaction between underlying medical conditions and treatment modalities in the etiology of iatrogenic infertility

7. Investigate occupational exposures. (This section in large part reflects the recommendations for prioritizing research in reproductive health made in the National Occupational Research Agenda (17, 50).) Conduct research to better define the contribution of workplace exposures and workplace factors on the incidence of adverse outcomes such as infertility, pregnancy loss, pregnancy complications, and congenital malformations.
a. Improve research methods
i. Develop new, more rapid methods to screen large numbers of chemicals and to identify those that are potential reproductive hazards.
ii. Conduct research to improve exposure assessment including research on biomonitoring methods, control technologies, and interventions.
iii. Improve retrospective exposure assessment methods for use in case-control studies of rare adverse reproductive outcomes, such as congenital anomalies.

iv. Develop standard occupational history tools for use by clinicians and promote their use
v. Improve surveillance methods to identify potential workplace risk factors, for example, through the development of automated North American Industry Classification System (NAICS) codes for standard birth records (e.g., birth certificates).

b. Investigate exposures
   i. Develop a strategy for prioritizing epidemiologic and intervention research on workplace exposures, according to the results of laboratory studies, by:
      1. developing new methods to screen large numbers of chemicals
      2. validating the new methods by testing their ability to appropriately classify the toxicity of known toxicants and nontoxicants
      3. applying the new methods to chemicals of unknown activity
      4. using the results of new methods to prioritize chemicals for more comprehensive, traditional toxicity testing in model species, followed by field studies for those compounds for which human exposure is high or widespread
   ii. Conduct studies of high priority exposures to identify and quantify risk of adverse reproductive health associated with workplace exposures.
   iii. Develop accurate screening tools for assessing exposure to reproductive toxins
c. Foster the dissemination of information and technologies to protect the reproductive health of workers by transfer of research findings, technologies, and information into practice

8. Investigate environmental exposures
   a. Design and conduct health studies
      i. Study low doses (environmentally relevant doses), chemical mixtures (patterns of exposure), long latency periods, exposures during specific life stages and genetic susceptibility
      ii. Study the effect of endocrine disrupting chemicals (EDCs) (bisphenol A, phthalates) on gene imprinting
      iii. Focus on high priority compounds: those under-investigated, bioactive at low doses, with potential widespread exposure due to biological persistence or continuous use (heavy metals, PCBs, hormonally active agents, brominated flame retardants)
   b. Explore possible effect modifiers on the association between environmental exposures and infertility outcomes such as:
      i. Age, gender, race/ethnicity, occupation, SES
      ii. Nutritional status and obesity; infections
      iii. Behaviors, pharmaceutical use

c. Determine biologically active exposure levels
    i. Study levels in individuals from conception to adulthood years
    ii. Determine the thresholds of lead, cadmium and mercury above which fertility becomes impaired
    iii. Develop additive, multiplicative or other models of interaction among multiple concurrent exposures and examine how concurrent exposures modify the biologically active levels of individual exposures
d. Assess human exposure levels
    i. Determine valid measurements which are representative of the population
e. Develop instruments for assessing infertility risk (occupational histories, risk behaviors, personal care products, use of plastics in the home and other EDCs, other)
f. Understand the role of diet in infertility
    i. Soy products
    ii. Other sources of phytoestrogens
    iii. Herbal preparations and other nutritional supplements

9. Develop and evaluate interventions targeted to youth and young adults
    a. Advocate condom use, delayed debut of sexual intercourse, and other interventions such as non-penetrative intercourse to reduce the incidence of STDs, and use of highly effective contraception for prevention of teen pregnancy and unintended pregnancy (dual use)
    b. Reconcile the messages for infertility prevention, prevention of unintended pregnancy and HIV/STDs among youth
    c. Assess the impact of programs aimed at preventing alcohol and recreational drug use, tobacco use and of those improving nutrition and physical activity on lowering risk of infertility
10. Address the specific research needs for the prevention of male factor infertility
    a. Establish better methods and techniques to measure semen quality and function
    b. Assess the impact of recreational and prescription drug use
    c. Examine occupational exposures
        i. Outdoor workers and effect on semen quality
        ii. Studies on high dose exposures at indoor workplaces and semen quality
    d. Examine environmental exposures
        i. Air pollution and effect on semen quality
        ii. Environmental exposures and hypospadias
    e. Assess varicocoele as a primary cause
    f. Review epidemiologic and clinical studies of Testicular Dysgenesis Syndrome, its etiology (parental behaviors, environmental exposures) and sequelae (cryptorchidism, hypospadias and other genitourinary malformations, reduced semen quality/ sub-fertility/infertility, testicular cancer)
11. Investigate genetic influences on infertility

a. Identify genes and polymorphisms associated with infertility and recurrent pregnancy loss
    i. Conduct Human Genetics and Epidemiology (HuGE) reviews
    ii. Study paternal factors and recurrent pregnancy loss
b. Determine epigenetic abnormalities leading to infertility

12. Study trans-generational and in-utero effects
    a. Assess effects of environmental and occupational exposures, lifestyle and health behaviors during the preconception period or during pregnancy on the fertility and fecundity of the offspring
    b. Assess effects of infertility of the parents on the fertility and fecundity of the offspring
    c. Determine effect of infertility treatment on the fertility and fecundity of the offspring
    d. Determine effectiveness of preconception care and prenatal care programs in preventing infertility and subfecundity in the offspring
13. Investigate other causes
    a. Examine immune mechanisms of infertility and recurrent pregnancy loss, including those mechanisms triggered by occupational and environmental toxicants
    b. Examine effects of hypothyroidism
14. Conduct communication research
    a. Understand differences among potential target groups
    b. Identify and prioritize communication topics
15. Conduct psychological research
    a. Psychosocial determinants (e.g., fertility goals) as modifiers of risk behavior change
    b. Determine emotional support needed to adhere to risk reduction strategies
16. Address other research needs
    a. Conduct cost-effectiveness and cost-benefit analyses for the implementation of infertility primary prevention programs

C. Research needed for secondary prevention

1. Improve early detection of infertility
    a. Develop and evaluate methods for detecting reduced fertility at an earlier age, and at earlier stages of the disease process
    b. Evaluate biomarkers of reduced ovarian reserve
    c. Assess semen quality
    d. Develop a screening tool to periodically measure fertility potential
2. Conduct communication research
    a. Understand differences among potential target groups
    b. Identify and prioritize communication topics
3. Conduct psychological research
    a. Assess impact of early detection of infertility on well being and quality of life

b. Psychosocial determinants (e.g., fertility goals) as modifiers of service-seeking behavior
c. Determine emotional support needed to seek diagnosis
d. Psychological issues surrounding decision making about seeking infertility assessment

4. Address other research needs
    a. Conduct cost-effectiveness and cost-benefit analyses for the implementation of early infertility detection programs

D. Research needed for tertiary prevention

1. Evaluate the safety and efficacy of infertility treatment
    a. Assess fertility drugs
        i. Conduct clinical trials of alternative ovulation induction regimens
        ii. Enhance detection of susceptibility to drugs to prevent ovarian hyperstimulation syndrome
        iii. Assess the effect of adjuvant therapy (baby aspirin) in enhancing success rates of IVF
    b. Improve methods to preserve the integrity of oocytes and embryos
        i. Evaluate embryology laboratory techniques and products (e.g., culture media)
        ii. Advance knowledge on morphological and genetic characteristics that predict successful implantation and live birth (pre-implantation genetic diagnosis (PGD), and screening (PGS), comparative genomic hybridization (CGH), comprehensive chromosome screening (CCS))
        iii. Develop and evaluate embryo selection strategies based on proteomics or metabolomics to support elective single embryo transfer
    c. Design and conduct safety studies
        i. Assess long term adverse health outcomes for women who have received infertility treatment (whether treatment was successful or not) and of children conceived as a result of infertility treatment
        ii. Conduct post marketing studies on drugs. CDC and FDA should consider collaborating on the conduct of research studies on the adverse effects of infertility treatment.
        iii. Evaluate the impact of infertility treatment on birth defects and developmental disabilities
        iv. Examine cancer as an adverse outcome
        v. Investigate ICSI and Y chromosome deletion
        vi. Investigate ICSI and other outcomes in children
        vii. Disentangle the adverse effects of treatment from the effects of the underlying infertility
    d. Address insurance-related issues
        i. Conduct comparative cost-effectiveness research on

treatment alternatives
        ii. Develop and test mixed-method approaches to facilitate access to care and eliminate disparities
        iii. Study single embryo transfer as related to access to insurance
        iv. Evaluate patient outcomes, including multiple births, as related to insurance
        v. Coordinate the development of insurance benefit packages with professional guidelines
    e. Conduct cost/benefit analyses using data from sources such as the Infertility Prevention Project administered by the Division of STD Prevention in CDC's National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
        i. Update and gather accurate cost data
        ii. Conduct conjoint analysis to assess user preference about medical interventions.
    f. Development and assess low-cost ART
2. Evaluate the safety and efficacy of third party reproduction
    a. Oocyte donation
    b. Oocyte cryopreservation
    c. Sperm donation
    d. Reproductive tissue donation/transplant
    e. Gestational surrogacy
    f. PGD and PGS
3. Conduct communication research
    a. Understand differences among potential target groups (e.g., cancer survivors, HIV-positive persons, ethnic/racial minorities, gay/lesbian/transgender groups, providers, decision makers, media, and general public)
    b. Identify and prioritize communication topics (e.g., genetic conditions, risks and benefits of multiple embryo transfer)
4. Conduct psychological research
    a. Assess impact of infertility on well being and quality of life
    b. Measure the strength of the desire for a biological child
    c. Psychosocial determinants (e.g., fertility goals) as modifiers of service-seeking behavior
    d. Assess the impact of multiple gestation and adverse pregnancy outcomes on parents and children
    e. Determine emotional support for parents and children
    f. Psychological issues surrounding decision making about stopping treatment or forgoing adoption
    g. Conduct psychological assessments of oocyte donors and impact of donation
    h. Conduct psychological assessment of candidate gestational surrogates before the experience and of surrogates after a variety of pregnancy outcomes
5. Address other research needs

a. Examine Characteristics of those not seeking treatment
b. Assess treatment of recurrent pregnancy loss
c. Develop individually tailored infertility medications

V. ADVANCING POLICY: DEFINING THE ISSUES AND FINDING THE NEEDED SOLUTIONS

A coherent National Action Plan must be based on a framework that ensures the right questions are asked, the right evidence is collected using rigorous scientific methods to answer the questions, and the scientific knowledge is rapidly disseminated and translated into public health programs according to evidence-based priorities. In the area of infertility, key policy making issues are related to the racial and economic disparities in the distribution of risk factors and in the ability to access preventive services, diagnosis and treatment of infertility, and alternative family building options such as adoption. The specific roles and responsibilities of federal agencies, state and local governments, health care providers, insurance companies, workers' representatives, and consumer organizations need to be clarified. An effective communication program is also needed to ensure that the necessary information is distributed to policy makers, stakeholders such as health care providers, insurance companies, workers' representatives and consumer organizations, and the general public, so that programs are acceptable to all parties and effective in achieving their objectives. Public/private organizations and the not for profit sector should be involved in developing strategies to turn evidence into public health policy, treatment guidelines and messages to reduce the burden of infertility and maximize benefit for individuals and for society.

A. Policy development

1. Defining infertility
    a. Assess whether infertility is a disease, disability, disorder or some combination
    b. Solicit the endorsement of a broad coalition of stakeholders
    c. Discuss the following ideas:
        i. Use the ASRM definition as a starting point to define infertility
        ii. Weigh advantages of defining infertility as a disease/disability from perspective of Americans with Disabilities Act (ADA) (moral and legal protection, prohibition of discrimination under the ADA), against its drawbacks (many individuals may be uncomfortable with being labeled as "diseased" or "disabled")
        iii. Recognize that certain groups (e.g., cancer patients, same-sex couples, HIV-discordant couples, those seeking posthumous conception) may not fit the definition of "infertile".
        iv. Reach consensus from a policy perspective for the purpose of guiding insurance coverage

v. Clarify the relation between infertility as a disease and infertility as the result of advancing age.
vi. Discuss secondary infertility
vii. Others

2. Gathering Evidence: surveillance and research
    a. Improve the current surveillance of ART
        i. Allow improved tracking of multiple ART cycles of the same patient
        ii. Expand surveillance to maternal and infant outcomes by linking ART records with vital records, administrative health records and disease registries
    b. Promote legislation to mandate surveillance on the safety and efficacy of non-ART infertility treatment
    c. Ensure adequate resources for the implementation of the Fertility Clinic Success Rate and Certification Act
    d. Maintain the vital statistics system and strengthen the components that are relevant to the measurement of infertility and the assessment of outcomes of infertility treatment
    e. Ensure that the research agenda addresses public health priorities and that adequate resources are allocated to pursue its objectives
3. Translating science into programs
    a. Develop systems and policies to facilitate translation of research results into prevention programs
4. Integrating infertility and impaired fecundity into public health services
    a. Incorporate infertility prevention in a broader sexual and reproductive health promotion agenda for both men and women
    b. Address disparities in public health resources for pregnancy prevention and infertility treatment through public financing of comprehensive reproductive health services that integrate family planning with programs assisting infertile patients
        i. Infertility prevention programs targeting obesity, STDs and environmental exposures that reduce fertility
        ii. Incorporate preconception care
        iii. Address insurance coverage gaps
    c. Promote public financing of infertility screening and assessment
        i. Low-income patient would not avoid these tests due to inability to pay
    d. Develop outreach efforts to ensure access to services
5. Address healthcare financing
    a. Insurance coverage
        i. Design benefits to maximize access and minimize adverse/costly health outcomes such as those associated with multiple deliveries
    b. Medicaid coverage
        i. Design a cost-effective infertility diagnosis and treatment benefit for recipients of Medicaid coverage throughout the nation
6. Addressing ethical Issues pertaining to the provision of infertility services

a. Develop a national framework for egg donation
    i. Establish fair and non-coercive compensation of donors
    ii. Address differences between donation to infertile couples and donation for infertility treatment and scientific research
    iii. Develop evidence-based guidelines that minimize the risk of adverse health consequences of repeated egg donation by healthy volunteers
b. Address ethical issues surrounding gestational surrogacy
c. Balance the reproductive interest of infertile couples in having children born through ART or other forms of treatment with the societal interest in preventing adverse health outcomes and excessive health care costs
    i. Cost of special education or other interventions vs. benefit to parents having children that otherwise would not have been born
d. Address advancing maternal age
    i. Review the principles that should guide the application of technologies that expand the normal biological range for human activities such as conceiving or carrying out a pregnancy
e. Review the impact that ethical and legal issues surrounding infertility treatment have on public health programs and policies

B. Evidence-based patient care guidelines

1. General recommendations
    a. Review and update existing evidence-based practice guidelines ; promote guideline awareness and adherence among heath care providers
    b. Ensure that guidelines are developed with input from all stakeholders, including insurance companies and consumer organizations
    c. Develop strategies to promote adherence to recommendations to prevent infertility by all stakeholders
        i. Screen and treat STDs that result in infertility
        ii. Treat of sexual partners for STDs
        iii. Promote primary prevention
2. Providers
    a. Deliver consistent evidence-based guidelines to providers who screen and treat STDs.
        i. Strategies to effectively communicate with various groups of patients (by age and other demographic characteristics)
    b. Develop guidelines for physicians who provide treatment to cancer patients using the American Society for Clinical Oncologists' (ASCO) recommendations as a starting point
        i. To systematically assess infertility risk based on type of cancer, age at diagnosis, treatment received and baseline fertility potential
        ii. To provide comprehensive counseling on fertility preservation methods available to the patients

c. Increase awareness of potential risk factors and promote gathering male and female patients' history of residence, occupations and hobbies that might have exposed them to contaminants that affect fertility, e.g., personal care products, food can liners, pesticides, other endocrine disruptors
d. Access provider perspectives on provision of infertility treatment and services to individuals of all sexual orientations and develop appropriate strategies for reducing barriers to treatment
e. Develop tools for providing emotional assistance to infertile women and men, particularly those with no interest in reproduction by donor gametes or embryos
    i. Evaluate need for mental health referral and facilitate access to mental health care for patients who need it

3. Youth
    a. Develop guidance for physicians to counsel youth about risk factors (obesity, tobacco smoking, illicit drug use, occupational and environmental hazards, STD risks/prevention interventions, aging) for infertility
        i. Develop fertility preservation/infertility prevention messages that may appeal to young people who are not interested in having children in the near future
        ii. Adopt evidence-based approaches in promoting fertility-preserving lifestyles and behavior change when necessary.
        iii. Increase awareness of the link between STDs in youth and infertility later in life without interfering with the promotion of effective means for the prevention of unintended pregnancy
    b. Develop guidance to emphasize the need for early diagnosis of conditions that lead to infertility
        i. STDs and PID
        ii. Obesity and the metabolic syndrome
        iii. Endometriosis
        iv. PCOS
        v. Tobacco smoking and POI
    c. Develop guidance for counseling young women who are considering egg donation or gestational surrogacy
4. Male Infertility
    a. Promote awareness that screening for infertility by a urologist may lead to diagnosis of a number of related and underlying conditions
        i. Occult testicular and prostatic cancer during infertility workup
        ii. Retrograde ejaculation and undiagnosed diabetes
        iii. Erectile dysfunction and risk for CVD or small artery disease
        iv. Cystic fibrosis and other genetic conditions
        v. Others
    b. Promote taking an occupational history in the clinical assessment of infertility, to increase the likelihood of identifying exposures that can be removed or reduced
5. Infertility Treatment

a. Develop guidelines to counsel infertile couples, addressing:
    i. Coping with the process
    ii. Risks and benefits of treatment
    iii. Health consequences of singleton vs. multiple pregnancies
    iv. Coping with treatment failure
    v. Adoption
    vi. Child-free living
    vii. Special considerations for vulnerable subgroups (cancer patients, people living with HIV, etc.)
b. Develop uniform requirements for patient informed consents to ensure that risks and benefits of treatment are described in a balanced, evidence-based framework, and that appropriate warnings are given when evidence is inadequate to assess the efficacy or safety of specific drugs, devices or procedures. The informed consent should also disclose conflicts of interest arising from the provider's conduct of research on infertility treatment or from financial interest in the success of a product. Informed consent processes should be developed both for infertility patients and for donors of gametes and embryos.
c. Develop evidence-based guidance for optimizing parameters of ovarian response during gonadotropin stimulation cycles
d. Develop evidence-based guidance for the maximum number of ovarian stimulation and intrauterine insemination procedures before proceeding to ART

6. Access to care/disparities
    a. Increase involvement of physicians in communities to strengthen access to care
    b. Increase outreach to minorities, as these groups are disproportionately affected by many infertility risk factors, including chlamydia, obesity and certain occupational exposures
    c. Develop strategies to remove financial and non-financial barriers to seeking infertility care

C. Dissemination of information and education of target groups and general public

1. Communication
    a. Expand messages to promote reproductive health, family planning, and safe motherhood, including preconception care
        i. Include fertility preservation messages
        ii. Increase awareness that infertility may be preventable, and
        iii. Include information about options for overcoming infertility
    b. Develop culturally appropriate messages increasing the awareness that normal aging processes place a limit to the ability to procreate, and that postponement of childbearing may reduce fertility.
    c. Develop an inventory of existing health messages pertaining to infertility awareness and fertility preservation

d. Identify effective strategies to market and deliver messages to young males and females
e. Foster the dissemination of information and technologies to protect the reproductive health of workers (from the National Occupational Research Agenda).
    i. Transfer research findings, technologies, and information into practice by publishing in technical and trade journals and enhancing stakeholders' capacity to apply laboratory and field deployable methods and technologies.
    ii. Improve the quality of reproductive health information on material safety data sheets (MSDSs)
    iii. Foster partnerships and coordination of the reproductive health research activities within and outside the federal government, including affected employers and workers, to prevent adverse reproductive health outcomes.
f. Foster the dissemination of information on environmental exposure known to interfere with reproduction, including exposures within the household
g. Develop fertility preservation messages targeting key populations
    i. Combined with prevention of unintended pregnancy where appropriate
h. Develop messages for non-English speaking populations
i. Engage all stakeholders in promoting primary prevention messages
j. Use media messaging to increase access to infertility care and treatment
k. Develop and promote training opportunities and aid materials
l. Develop and disseminate evidence-based messages to inform the general public about the frequency, causes, signs and consequences of infertility
m. Develop and disseminate culturally appropriate evidence-based recommendations on diagnostic, treatment options and management (including adoption and child-free living)for infertile couples and individuals
n. Raise public awareness about the impact of STD on infertility through national media campaigns.
o. Identify and exploit social media (blogs, social networks, etc) commonly used by people who experience infertility to provide information and support
p. Develop messages to reduce stigma associated with infertility and improve public understanding of, and support for, people who live with infertility.

2. Education
    a. Employ the strong evidence base available to support a national public education campaign on STD and tobacco prevention interventions for infertility prevention.
    b. Increase awareness of the effect of aging on fertility.
    c. Develop messages increasing awareness of occupational and environmental exposures that affect fertility, as appropriate
    d. Engage mass media as key partners to sustain the national effort to define infertility as a public health issue

e. Develop strategies for countering the advertising of alcohol, tobacco and unhealthy foods in movies and televisions programs.
f. Expand reproductive health education efforts for young men and women by adding a fertility preservation focus.
g. Develop racial/ethnic/linguistic-appropriate information and education about infertility care and treatment.
h. Target education efforts to identify and address knowledge gaps on infertility at appropriate stages in life
    i. STD information to adolescents, younger or older persons
    ii. The best age and way to discuss infertility with women and men
    iii. Maintaining fertility while preventing unintended pregnancy
    iv. The impact of postponement of childbearing on fertility
    v. Challenge of discussions about the impact and choices related to cancer treatment and fertility in person diagnosed with cancer prior to childbearing years (e.g. children and young adults)
i. Develop effective messaging, communication, education and outreach targeting young men and addressing infertility and reproductive health issues
    i. Anabolic steroids
    ii. Recreational and prescription drugs
    iii. Occupational exposures.
j. Educate the general public on strategies to minimize the risk of infertility
k. Educate population groups at risk for infertility and poor pregnancy outcomes on their reproductive risks, options to overcome infertility, and strategies to minimize the risk of adverse outcomes of infertility treatment
l. Develop strategies to reduce stigma associated with infertility while promoting attitudes and behaviors that facilitate early access to infertility diagnosis and treatment
m. Assess the feasibility of integrating infertility education into existing national reproductive health education

VI. STRENGTHENING CAPACITY: TRANSFORMING THE ORGANIZATION AND STRUCTURE OF PUBLIC HEALTH AGENCIES AND PARTNERSHIPS

This aspect of the plan was not developed in the “white paper” (4) and was discussed only briefly during the National Symposium. Further discussions within the CDC Infertility Working Group and expert feedback on early drafts of this Outline provided the material necessary to develop this section. Effective actions to prevent infertility may require a transformation in how public health agencies have addressed infertility. Strengthening the competencies and resources of the public health workforce for the needed tasks and managing the development, maintenance, and dynamic growth of effective partnerships are necessary for this change. Public health agencies must develop and maintain new capacities, including organizational arrangements and

competencies for infertility prevention. They also need networks of established and innovative partnerships to reach goals set forth in this plan.

A. Expanding services

1. Primary Prevention Services
    a. Expand the capacity of the CDC Infertility Prevention Program to support screening services for STDs and improve screening service delivery.
    b. Promote the prevention of environmental exposures
        i. By increasing public health laboratory services that can conduct biomonitoring
        ii. By minimizing exposures to EDCs (personal care products, can liners, pesticides, etc.)
    c. Ensure that pediatricians and school health educators and providers have adequate knowledge on the prevalence and causes of infertility among youth, and have adequate resources to include appropriate prevention messages for children and their parents in their counseling and teaching activities.
    d. Ensure that school programs have adequate knowledge and resources to promote healthy nutrition and the prevention of tobacco smoking, alcohol and recreational drug use, and include information about the impact of obesity, tobacco smoking and recreational drug use on fertility
    e. Include other entities, such as community-based organizations and houses of worship in dissemination/education plans
    f. Promote the prevention of occupational contribution to infertility by teaching, extending and communicating knowledge to affected workers taking as a model the NIOSH- sponsored review of healthcare worker exposure to hazardous drugs leading to the Alert on safe handling of hazardous drugs in healthcare (51).
2. Secondary Prevention Services
    a. Ensure adequate counseling and screening for infertility and referral for infertility services at Title X clinics.
    b. Enhance primary care services for women and men of reproductive age by disseminating information on infertility prevention and detection among people who are trying to conceive
3. Tertiary Prevention Services
    a. Ensure that reproductive endocrinologists and health professionals engaged in the treatment of infertility have adequate resources and training to educate patients about the risk of adverse maternal and child health outcomes and about the potential advantages of single embryo transfer.

4. Infertility Care Services
    a. Ensure that training programs for health professionals recruit and graduate sufficient numbers of professionals to support the expanded demand for infertility detection and management promoted by the Plan
    b. Ensure that reproductive health care professionals are adequately trained to implement cost-effective protocols for the diagnosis and treatment of infertility
    c. Ensure that reproductive health care facilities are adequately equipped to implement cost-effective protocols for the counseling of patients, for the diagnosis and treatment of infertility, and can facilitate referral to specialized care for patients in need of more advanced services
5. Educating Youth
    a. Coordinate with school health programs to address the risk factors of tobacco use and nutrition/obesity
    b. Create specific programs to include concerns about reproductive future

B. Organizational transformation and partnership building

A comprehensive effort to build the capacity necessary to address infertility in the U.S. may require a re-alignment of the roles and responsibilities of federal, state, local and tribal government agencies and the establishment of new partnerships with professional and consumer organizations, and with industry. The following are some of the conditions that may be needed to implement these changes:

1. Infertility is poorly addressed by categorical legislation (e.g., tobacco control, support for cancer survivorship), because it results from many risk factors and is associated with a variety of medical conditions, and it is not necessarily the most severe adverse health effect of an exposure (e.g., tobacco) or the most disabling effect of a medical condition (e.g., obesity)). To effectively address the public health impact of infertility, the traditional categorical approach to policy making and organization of services needs to be abandoned in favor of strategies that promote comprehensive primary prevention (health and wellness promotion), integration of services, and coordination of public outreach messages across agencies.
2. The infertility prevention focus must be adopted by agencies with very different missions and organizational structures. For example, the NIH could consider allocating resources to infertility in child and adult cancer patients, while the Department of Defense (DOD) could consider addressing fertility preservation among women and men who serve in military combat.
3. Federal agencies such as the CDC and the NIH should establish interagency consultations involving experts from multiple disciplines to ensure that basic and clinical research are prioritized to address public health priorities. A coordinated plan will also ensure that state-of-the-art science is employed to address a

variety of topics that affect infertility as a public health problem, including smoking, obesity, health disparities, STDs and stigma.

4. The scientific and programmatic capacity of states, territories, and tribal governments needs to be enhanced to develop the local expertise necessary to address the complex issues associated with the prevention, detection and management of infertility. This can be accomplished by promoting state, tribal and local-level partnership between government agencies, academic institutions and professional organizations, and by promoting partnerships between federal and state government agencies. Where such partnerships already exist, infertility should be included on the agenda.
5. Decision makers at all levels of government need to be informed about the needs and priorities in the areas of surveillance, research, and health care, including policy and financing needs, and about the scientific evidence at the basis of strategies for addressing infertility. To this end, it is necessary to develop a communications/education plan for political decision makers.
6. Building the capacity necessary to implement the National Action Plan is not feasible without the support and participation of a broad coalition of stakeholders, and the design, implementation and evaluation of the Plan must be the product of a national dialogue expanded to the broadest possible range of partners.
7. Infertility is an important public health issue not only in the United States, but also globally. Regional and global partnerships in infertility present important opportunities for collaboration. Research and policy development in other countries are important for the United States and have been considered in the development of this outline. Communicating closely with regional and global partners regarding their experiences with policies and programs in diverse settings is likely to be beneficial
    a. The United States should thoroughly review lessons learned and experiences from other countries that have defined infertility as a public health issue. (e.g.: integration of infertility detection and care in national health systems, and production of evidence-based regulation and guidelines pertaining to infertility treatment in European countries)
    b. The United States should provide world leadership in addressing reproductive hazards in the workplace through development of new methods, formation of research collaborations and communication of research findings(from the National Occupational Research Agenda)

C. Stakeholders

We recognize the following categories of organizations as potentially interested in the development of the National Action Plan, and capable of participating in the implementation of the plan. Appendix B (section X) contains a list of organizations that participated in the symposium and review process or have expressed in working on the National Action Plan. We welcome feedback and active participation in this effort by these and other organizations that may have been omitted from the list. We also recognize that individual infertility service providers, consumers and the community at large hold important stakes in the development and implementation of

the National Action Plan: we are committed to circulate the National Action Plan as broadly as possible to obtain input representing a balanced variety of perspectives

1. Federal government
2. State, territorial, tribal and local government
3. Policymakers
4. Academic institutions
5. Professional organizations
6. Consumer organizations
7. Other not-for-profit organizations
8. Health insurance industry
9. Pharmaceutical industry

VII. TAKING ACTION: PUTTING PRESENT KNOWLEDGE TO WORK

This section addresses one of the major questions asked at the National Symposium on Infertility ("On the basis of what we already know, what can be done now?") Listed below are action items that can be taken now to reduce the burden of infertility. All stakeholders should be involved in the development and implementation of action items. Finalizing the list will require prioritizing the items, estimating the resources needed to implement each item, assessing plausible timelines, and identifying appropriate outcomes and measures for evaluating impact.

A. Actions for developing and maintaining the plan

1. Establish a broad coalition of stakeholders that will take responsibility for the plan.
2. Establish a working group to review the goals proposed in this outline, specify an initial set of goals for infertility detection, management and prevention to be included in the national action plan, and periodically assess progress toward the goals as well as the need for revisions of the plan.
3. Promote the integration of infertility-related goals into other public health action plans and programs. As many government agencies and nongovernmental organizations track the health status of the U.S. population by making reference to the Healthy People Goals (e.g., Healthy People 2010, now being revised for the next decade) it is appropriate that key, measurable goals for the control of infertility and recurrent pregnancy loss be developed and incorporated in the same framework.
    a. The following is a proposed developmental goal for Healthy People 2020:
        i. To reduce the proportion of persons aged 18-44 years who have impaired fecundity (i.e., a physical barrier preventing pregnancy or carrying a pregnancy to term).

B. Actions for evaluating impact

1. Establish an Infertility Surveillance Working Group whose task will include:

a. Expand the analysis of gaps in existing surveillance systems that was done in the white paper
b. Specify important population-based measures that are needed to establish baseline values and to monitor trends over time and across population subgroups
c. Propose new data collection to fill those gaps, either through enhancement of existing systems or development of new systems
    i. Adding data collection elements to existing systems
    ii. Linkage of existing data systems
    iii. Surveys
    iv. Ad hoc studies

C. Actions for primary prevention

1. Expand reproductive health education/information programs to integrate awareness of the prevalence and causes of infertility among youth with messages promoting STD and unintended pregnancy prevention.
2. Develop interventions targeting adolescents and focusing on preserving fertility and wellness through smoking cessation and prevention of other risk factors such as obesity and STDs
3. Chlamydia screening: Improve screening (and treatment), evaluate effectiveness and develop interventions to reduce the impact of stigma among individuals in need of STD screening. Develop and promote home-based screening.

D. Actions for secondary prevention

1. Develop programs to facilitate access to infertility screening and testing services and minimize delays in access to care among:
    a. Women and men younger than 35 years of age who fail to naturally conceive within 12 months, and
    b. Women and men 35 years of age or older who fail to naturally conceive within 6 months

E. Actions for tertiary prevention

1. Promote the development and adoption of professional guidelines that minimize the risk of adverse pregnancy outcomes following successful treatment of infertility
2. Develop education/information programs to increase awareness of the risk of adverse maternal and child health outcomes of all forms of infertility treatment and of the potential advantages of single embryo transfer among women who use assisted reproductive technology and are considering multiple embryo transfer.

3. Reduce financial barriers to access to elective single embryo transfer among women who conceive using assisted reproductive technology and have a high probability of establishing a pregnancy because of a good prognostic profile (i.e., a high expected probability of success with ART, as indicated by age under 35 years, no history of failure with ART, and the production of multiple embryos of good quality).
4. Assure and continuously assess the coordination between health insurance policy and professional guidelines

F. Actions for policy and guideline development

1. Hold a summit of the essential stakeholders to clarify the definition of infertility as a disease, disability or quality of life issue and explore the implications of the definitions for insurance coverage and public financing of care.
2. Develop and test age/race/ethnic/linguistic-appropriate sex education messages and launch a comprehensive campaign targeting school-age children. Planned Parenthood has a wealth of experience in this area and should be engaged as a key partner, including schools, community-based organizations and houses of worship.
3. Establish a committee with representation by all stakeholders to analyze the ethical implications and the psychosocial and medical consequences of current infertility care practices

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IX. APPENDIX A

Existing surveillance systems collecting data on infertility and reproductive health

National Survey of Family Growth

National estimates of the prevalence of infertility and impaired fecundity, as well as use of infertility services, are obtained through the National Survey of Family Growth (NSFG). The NSFG gathers information on family life, marriage and divorce, pregnancy, infertility, use of contraception, and men's and women's health. The survey results are used by the U.S. Department of Health and Human Services and others to plan health services and health education programs, and to do statistical studies of families, fertility, and health (http://www.cdc.gov/nchs/NSFG.htm). The NSFG has relatively small samples for tracking the use of ART or other forms of infertility treatment over time and only collects limited data on the timing of visits. Thus, it is likely that additional data collection will be needed to evaluate the impact of policies and programs at the state or local level and to study variation across states.

National ART Surveillance System

The National ART Surveillance System (NASS) is a Web-based ART data reporting system supported by the CDC and in large part based on data collected by SART. The data collected include information on the client's medical history (such as infertility diagnoses), clinical information pertaining to the ART procedure, and information on resulting pregnancies and births. The data file is organized with one record per ART procedure performed. Multiple procedures from a single patient are not linked. It is estimated that the ART surveillance system captures over 95% of the ART procedures performed each year in the U.S.

Despite its completeness and the rich data base, the ART surveillance system is intrinsically limited in its ability to follow up mothers and their ART-conceived infants. In particular, data about specific obstetric, perinatal, and neonatal complications and outcomes cannot reliably be collected with the current ART surveillance system because ART providers do not typically care for patients beyond their first trimester of pregnancy. CDC has developed collaborative projects with three state health departments to link the existing ART surveillance data for infants born to resident women with data obtained from the state birth and death certificate files. Extension of this project to a sufficient number of states could result in a surveillance system for the perinatal outcomes of ART.

Another major limitation of NASS is that multiple ART procedures of the same patient cannot be linked to evaluate the cumulative success rate (total reproductive potential). Technical solutions to this problem will improve the ability to evaluate the effectiveness of the ART.

Behavioral Risk Factor Surveillance System

The Behavioral Risk Factor Surveillance System (BRFSS) is a state-based system of health surveys coordinated by the CDC that collects information on health risk behaviors, preventive health practices, and health care access primarily related to chronic disease and injury. Data are collected monthly in all 50 states, the District of Columbia, Puerto Rico, the U.S. Virgin Islands, and Guam. More than 350,000 adults are interviewed each year, making the BRFSS the largest telephone health survey in the world. States use BRFSS data to identify emerging health problems, establish and track health objectives, and develop and evaluate public health policies and programs. (http://www.cdc.gov/brfss/about.htm)

The CDC should evaluate the feasibility of adding infertility and use of infertility treatment to the BRFSS.

National Health and Nutrition Examination Survey

The NHANES program began in the early 1960s and has been conducted as a series of surveys focusing on different population groups or health topics. In 1999, the survey became a continuous program. This unique survey collects health and nutrition information on a nationally representative sample of about 5,000 persons each year. Household and private interview methods are used. The health interview topics include current health status, medical conditions, reproductive health (pregnancy history, lactation, use of contraception, and men's and women's health conditions), health insurance coverage, utilization of health care services, lifestyle behaviors (including sexual, illicit drug, alcohol, and tobacco use), and occupational history and environmental exposure to chemicals. NHANES is the cornerstone for national nutrition monitoring. As such the survey collects detailed dietary intake data, measured height and weight, and extensive blood and urine laboratory data. NHANES laboratory datasets and reports are produced on nutritional biomarkers, sexually transmitted diseases (STDs), and environmental chemicals. The survey results have been used to produce national estimates of obesity and overweight, STDs, and exposure to numerous environmental chemicals which may affect fertility and health. Although no information is collected on infertility, much of the current data collection is relevant to understanding health conditions and factors that affect fertility. The NHANES questionnaires and examination components are modified periodically as new topics of public health significance emerge. The feasibility of adding infertility and infertility treatment questions to future NHANES could be explored.

Pregnancy Risk Assessment Monitoring System

PRAMS, the Pregnancy Risk Assessment Monitoring System, is a surveillance project of the Centers for Disease Control and Prevention (CDC) and state health departments. PRAMS collects state-specific, population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy. The goal of the PRAMS project is to improve the health of mothers and infants by reducing adverse outcomes such as

low birth weight, infant mortality and morbidity, and maternal morbidity. (http://www.cdc.gov/prams/). PRAMS data collection now includes use of infertility treatment in selected states. This data may provide additional useful information on the association of infertility and infertility treatment with adverse perinatal health outcomes.

Birth Records

Birth certificates contain information on mother and father of infant, such as education, race, and age, and information about the infant, such as birth date, plurality, sex, birth weight, and congenital anomalies, complications of labor and delivery. The 2003 revision of the standard birth certificate includes information on use of infertility treatment and may become an important source of information on its maternal and child health correlates.

CDC should secure the resources necessary to purchase vital statistics data from states.

Infertility Prevention Program

CDC, in collaboration with the Office of Population Affairs (OPA) of the Department of Health and Human Services (HHS), supports a national Infertility Prevention Program (IPP), which funds and coordinates chlamydia screening and treatment services for low-income, sexually active young women attending family planning, STD, and other women's health care clinics (http://www.cdc.gov/std/infertility/ipp.htm). The surveillance component of the IPP gathers data that on the number of tests performed and the characteristics of the subject screened and the context of the visit during which the test was administered. These data contribute to the preparation of the Chlamydia Prevalence Monitoring Project Annual Report.

National Institute for Occupational Safety and Health

Occupationally and environmentally related diseases may not be readily identified if they produce a less severe, more common outcome, making them more difficult to detect against a low but predictable background of occurrence. Systematic collection of data makes identification of such relationships more feasible and cost effective.

NIOSH's National Occupational Hazard Survey and National Occupational Exposure Survey conducted in 1972–1974 and 1981–1983, respectively, has been used extensively to identify substances of common exposure (National Occupational Hazards Survey. Vol III. Survey Analysis and Supplemental Tables. DHHS (NIOSH) Publ no. 78–114. Cincinnati, OH, 1978; National Occupational Exposure Survey Analysis of Management Interview Responses. DHHS (NIOSH) Publ no. 89–103. Cincinnati, OH, 1988). These surveys are the only comprehensive assessments of general industry where the number of workers potentially exposed to chemical agents has been estimated. However, these databases are outdated and of limited use because they

indicate only potential exposure. Four current examples of NIOSH's addition of occupational information to data collections are summarized:

1. One of the most promising prospective studies that will add to our understanding of reproductive health is the National Children's Study (NCS), a multiagency landmark study of 100,000 children from preconception to adulthood (http://www.nationalchildrensstudy.gov). NIOSH NORA team members have partnered with NCS planners to provide guidance on how to include parental occupational histories as part of the baseline metrics of the cohort. This project will allow many hypotheses to be tested regarding parental exposures and their impact on congenital anomalies, developmental delays, sexual differentiation, puberty, and subsequent fertility.

2. NIOSH scientists are collaborating with the CDC National Center on Birth Defects and Developmental Disabilities and NCI to conduct an occupational exposure assessment using parental occupational information collected as part of the National Birth Defects Prevention Study (NBDPS) (http://www.nbdps.org). Parental exposures to solvents, metals, and pesticides will be analyzed, and estimated exposure among cases and controls will be compared.

3. The coding of parent's occupation and industry (O/I) can be collected on vital statistics records or national surveys of reproductive health. For example, the National Survey of Family Growth and the National Maternal and Infant Health Survey have limited O/I information. Although occupation and industry are part of the National Health and Nutrition Examination Survey (NHANES), this information cannot be linked with each pregnancy time period. Additional survey data could be added to NHANES and its updates, providing an opportunity for epidemiologic studies.

4. Parental occupation is recorded on birth and fetal death certificates in some states. NIOSH has supported efforts to include O/I on birth certificates in about 20 states and to develop software to reduce verbatim O/I information to Bureau of Census codes. The NIOSH Standardized Occupation/Industry Coding System software (SOIC) can be used for birth or death certificates and reduces verbatim O/I input to 1990 Bureau of Census codes with 86–88% success.

<u>Environmental Exposures Surveillance</u>

A. Surveillance of exposure to environmental chemicals.

National Report on Human Exposure to Environmental Chemicals

The National Report on Human Exposure to Environmental Chemicals (http://www.cdc.gov/exposurereport/) provides an ongoing surveillance of the U.S. population's exposure to environmental chemicals using biomonitoring. Biomonitoring is the assessment of human exposure to chemicals by measuring the chemicals or their metabolites in human specimens such as blood or urine. The list of chemicals includes hormonally active agents, such as bisphenol A, phthalates, pesticides, and persistent organic chemicals.

B. Surveillance of nutritional and biochemical indicators.

National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population

The National Report on Biochemical Indicators of Diet and Nutrition (1999-2002) (http://www.cdc.gov/nutritionreport/) is a first-of-its-kind report that provides a snapshot of the U.S. population's nutritional status by age, sex, and race/ethnicity. Using advanced laboratory science and innovative techniques, the Division of Laboratory Sciences at the Centers for Disease Control and Prevention (CDC), National Center for Environmental Health (NCEH) has been in the forefront of efforts to assess the nutritional status of the U.S. population through monitoring nutritional indicators. This Report improves our understanding of the levels of biochemical indicators of diet and nutrition in the general U.S. population and in selected subpopulations, such as children, women of childbearing age, and minorities.

Other data sources:

Office of Population Affairs
Human Resources and Service Administration
Health Information System database

X. APPENDIX B

The below list contains organizations that participated in the symposium and review process or have expressed interest in working on the National Action Plan for the Detection, Prevention and Management of Infertility.

Aetna
Agency for Toxic Substances & Disease Registry (ATSDR)
Albert Einstein College of Medicine
American Academy of Family Physicians (AAFP)
American College of Obstetrics and Gynecology (ACOG)
American Sexually Transmitted Disease Association (ASTDA)
American Social Health Association (ASHA)
American Society of Andrology (ASA)
American Society for Reproductive Medicine (ASRM)
American Urological Association (AUA)
Association of Maternal and Child Health Programs (AMCHP)
Association of Reproductive Health Professionals (ARHP)
Boston University
Boston Women's Health Book Collective (BWHBC)
Brown University
California Department of Health Services
Centers for Disease Control and Prevention (CDC)
Collaborative on Health and the Environment (CHE)
Department of Defense (DOD)
EMD Serono
Emory University
Environmental Protection Agency (EPA)
Family Health International (FHI)
Fertile Hope
Fertility Preservation Working Group (FPWG)
Florida Department of Health
Food and Drug Administration (FDA)
Harvard School of Public Health
Health Resources & Services Administration (HRSA)
International Committee Monitoring Assisted Reproductive Technologies (ICMART)
Lance Armstrong Foundation
March of Dimes Foundation
Massachusetts Department of Public Health
McMaster University
Michigan Department of Community Health
National Academy of Sciences/Institutes of Medicine (NAS/IOM)
National Coalition for Oversight of Assisted Reproductive Technology (NCOART)
National Coalition of STD Directors (NCSTDD)
National Institutes of Health (NIH)
Northwestern University

Office of Public Health and Science (OPHS)
Partnership for Prevention
Planned Parenthood Federation of America (PPFA)
Rachel's Well
Reproductive Health Technologies Project (RHTP)
RESOLVE: The National Infertility Association (RESOLVE)
University of Rochester
Rollins School of Public Health at Emory University
Society for Gynecologic Investigation (SGI)
Society for the Study of Male Reproduction (SSMR)
The American Fertility Association (The AFA)
The Environmental Working Group (EWG)
University of Alabama at Birmingham
University of California at Irvine
University of California, Los Angeles
University of California, San Francisco
University of North Carolina
University of Pittsburg
University of Washington
Virginia Mason University
Walter Reed Army Medical Center