

The sixth vital sign: what reproduction tells us about overall health.

Proceedings from a NICHD/CDC workshop

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STUDY QUESTION: Does the fertility status of an individual act as a biomarker for their future health?

SUMMARY ANSWER: Data support an association between reproductive health and overall health for men and women.

WHAT IS ALREADY KNOWN: Various chronic conditions, such as diabetes, obesity and cancer, can compromise fertility, but there are limited data for the converse situation, in which fertility status can influence or act as a marker for future health. Data reveal an association between infertility and incident cardiovascular disease and cancer in both men and women.

STUDY DESIGN, SIZE, AND DURATION: A National Institute of Child Health and Human Development-Centers for Disease Control and Prevention workshop in April 2016 was convened that brought together experts in both somatic diseases and conditions, and reproductive health. Goals of the workshop included obtaining information about the current state of the science linking fertility status and overall health, identifying potential gaps and barriers limiting progress in the field, and outlining the highest priorities to move the field forward.

PARTICIPANTS/MATERIALS, SETTING AND METHODS: Approximately 40 experts participated in the workshop.

MAIN RESULTS AND THE ROLE OF CHANCE: While the etiology remains uncertain for infertility, there is evidence for an association between male and female infertility and later health. The current body of evidence suggests four main categories for considering biological explanations: genetic factors, hormonal factors, *in utero* factors, and lifestyle/health factors. These categories would be key to include in future studies to develop a comprehensive and possibly standardized look at fertility status and overall health. Several themes emerged from the group discussion including strategies for maximizing use of existing resources and databases, the need for additional epidemiologic studies and public health surveillance, development of strategies to frame research so results could ultimately influence clinical practice, and the identification of short and long-term goals and the best means to achieve them.

LIMITATIONS, REASONS FOR CAUTION: Further research may not indicate an association between fertility status and overall health.

WIDER IMPLICATIONS OF THE FINDINGS: Currently medical care is compartmentalized. Reproductive medicine physicians treat patients for a short period of time before they transition to others for future care. Going forward, it is critical to take an interdisciplinary patient care approach that would involve experts in a broad range of medical specialties in order to more fully understand the complex inter-relationships between fertility and overall health. If infertility is confirmed as an early marker of chronic disease then screening practices could be adjusted, as they are for patients with a family history of malignancy.

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WHAT DOES THIS MEAN FOR PATIENTS?

This is a report from a workshop where a group of experts from around the world considered whether your fertility can tell you anything about how healthy you will be in the future.

It is known that some medical conditions, for example being obese, can have an impact on your fertility, but it is not clear whether your fertility may hold any clues to your future health. Recent studies have suggested that some causes of infertility may be linked with other health issues such as cardiovascular disease.

The expert group agreed that more research is needed before any conclusions can be drawn.

They suggested specific areas and strategies for future studies and noted that medical experts from diverse fields begin to incorporate reproductive health into more studies to help work out the nature of any possible relationships between infertility and overall health.

Introduction

It has been stated that ‘...different infertility etiologies not only share particular genes and/or molecular pathways with other pathologies but they have distinct clinical relationships with other diseases appearing after infertility is manifested’ (Tarin et al., 2015).

It is clear that chronic conditions such as cancer, diabetes and obesity can impair fertility (La Vignera et al., 2015; Mitchell and Fantasia, 2016; Silva et al., 2016). Indeed, any discussion of fertility status and the impact on future health must begin with the strong association between fertility status and current health (Sermondade et al., 2013; Eisenberg et al., 2016b; Sundaram et al., 2017). However, less is known about the extent to which fertility status can impact or act as a marker for future overall health. Infertility is not necessarily a unique disease of the reproductive axis, but is often physiologically or genetically linked with other diseases and conditions. Recent epidemiologic studies demonstrate links between fertility status in both males and females and various somatic diseases and disorders (Hotaling and Walsh, 2009; Eisenberg et al., 2014). Taken together, these data strongly suggest that fertility status can be a window into future health.

Data suggest that infertility may be associated with a variety of other health processes, suggesting infertility is genetically and clinically linked with these other diseases. For example, polycystic ovary syndrome (PCOS) has been associated with both impaired glucose tolerance and cardiovascular disease (Fauser et al., 2012). However, it is not clear whether if the symptoms of PCOS were lessened, differences in other health outcomes would result. Ovarian aging is also a reproductive process with potential for broader implications. The number of ovarian follicles peaks *in utero* and decreases throughout the lifespan of the woman. The question remains whether this pattern accelerates for women with decreased ovarian reserve, a condition of ovarian insufficiency associated with a lower response to gonadotrophin stimulation.

Decreased ovarian reserve is associated with genetic abnormalities and with shorter telomeres (Butts et al., 2009), a characteristic of age-related diseases.

It is important to remember that childbirth (and hence fertility) could affect maternal/women’s health in a positive direction (Falick Michaeli et al., 2015). High levels of endogenous estrogen and the physiological changes associated with breastfeeding are two factors related to pregnancy that might affect future health. In addition to the possibility of ‘rejuvenating effects’ of pregnancy, genetic dispositions may play a role in any correlation between pregnancy and overall health.

Subtle differences between males and females (e.g. physiology, hormonal) could affect the occurrence, severity or direction (protective or deleterious) of the effects of fertility status on overall health. Somatic diseases, such as, rheumatoid arthritis, autism and lupus, affect one sex more frequently than the other (Quintero et al., 2012; Rubtsova et al., 2015). Even in diseases with equal prevalence in males and females, there can be significant differences in severity; for example, men with dilated cardiomyopathy tend to die about 10 years before affected women (Herman et al., 2012). One intriguing possibility is that males and females read their genomes differently. Although scientific dogma maintains that Y chromosome genes only function in the gonad and that the second X chromosome is inactive in the female, these concepts are changing. In fact, 12 of 17 surviving genes on the Y chromosome have a broad tissue expression and hundreds of genes are expressed from the second X chromosome, also in a broad distribution pattern (Bellott et al., 2014). This leads to subtle, but distinct differences in XX and XY cells throughout the body. These findings lead to two clinically important implications for examining the impact of fertility status on overall health: first, the link between infertility and a given disease could manifest differently between the

sexes; and second, in cases where both sexes are similarly affected, there could be significant differences in severity. As such, specific emphasis on sex will be required for all fertility status and overall health studies and may require different methods of evaluation between the sexes.

If validated, the premise that fertility and overall health share common or intersecting physiological pathways, and that dysregulation of a common pathway can disrupt both systems, provides a valuable opportunity to affect future health during the fertility evaluation. Importantly, the directionality of the causal pathways between health and infertility are not definitively known at the current time. However, even if a cause and effect relationship remains unclear, the clinically relevant issue remains that a patient with infertility might also experience an increased risk of organ system dysfunction, apparent only later in life. Knowledge of the existence of such a relationship could provide an enormous opportunity for early detection, prevention, and intervention in serious, chronic diseases. With increased attention to infertility (Prevention, 2014), there is increased potential to reach people during their reproductive years, when they are highly motivated to protect their current and future health yet young enough to begin to make changes to their lifestyle/health, which may mitigate later disease risk. The lack of knowledge regarding the relationship between fertility status and overall health becomes even more important in light of the economic burdens of these chronic conditions and may increase further the issues of access to care for infertility evaluation and treatment.

Infertility is often the first health crisis faced by an otherwise healthy man or woman, but they might learn of a lifelong, non-reproductive condition from the clinician. Although achieving pregnancy is appropriately the first priority at the time, medical counseling about overall health should occur for both men and women, where a diagnosis of infertility could lead to a comprehensive look at overall health. If infertility serves as a window on future health, it could be a clinical 'game changer', providing new insights for the diagnosis of chronic disease and its underlying mechanisms. Clinical care would be transformed by early identification of those at risk for a disease (who otherwise may not know), in addition to treating those already diagnosed. Here, we focus on the primary disease outcomes (e.g. cardiovascular, cancer and metabolic) and etiologies (e.g. genetic) for which strong preliminary data are available.

Materials and Methods

Leaders at both the National Institute of Child Health and Human Development and Centers for Disease Control and Prevention convened the conference in April 2016 with interested parties from around the world. All participants made meaningful contributions to the workshop. The primary workshop organizers summarized the workshop and drafted the current report.

Results

Fertility status and cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death in men and women both globally and in the United States (Xu *et al.*, 2016). Current efforts focus on prevention of risk factors for CVD, frequently

targeting the late reproductive years, but aspects of reproductive development and health, including age at puberty, menstrual cyclicity and pregnancy (pre-eclampsia, gestational diabetes or pregnancy-induced hypertension) (Mosca *et al.*, 2011), lay the groundwork for subsequent cardiovascular health. Infertility itself, or underlying causes of infertility, could foretell of worsened CVD risk. If true, this would present a unique opportunity to identify high-risk individuals much earlier in life when intervention would be the most beneficial. Indeed, infertility and CVD share underlying biologic mechanisms, such as inflammation, as well as common risk factors, including late menarche, early menopause, PCOS, smoking, diet and adiposity.

The major risk factors for CVD are similar in women and men, including age, dyslipidemia, diabetes, hypertension, smoking, family history, obesity and physical inactivity. However, sex differences also are clinically significant (Vaccarino *et al.*, 1998; Gupta *et al.*, 2014). While deaths owing to CVD in the USA have substantially declined in both men and women within the last decade, there remains an inexplicable lack of improvement in survival from myocardial infarction among young women (Mehta *et al.*, 2016). These sex differences could be related to genetics, or hormonal status, both interesting variables that could tie back to reproductive health.

Validating the acceptance of the fertility status and overall health concept, the Framingham Heart Study (<https://www.framinghamheartstudy.org/>) recently added questions about female infertility and, 14% of respondents stated that they experienced infertility (in line with population estimates). Infertile women tended to be older and heavier than controls, but the number of live births and their other risk factors for CVD were similar.

The onset of CVD in women has a 10-year lag compared to onset in men. Studies suggest that reproductive variables in women, such as early menopause, premenopausal oophorectomy and primary ovarian insufficiency, are risk factors for CVD. Other reproductive factors influence risk of CVD, including the timing of menarche, pregnancy-associated hypertension and pre-eclampsia, gestational diabetes, PCOS, functional hypothalamic amenorrhea and the decline in ovarian function (Bleil *et al.*, 2013; Hillman *et al.*, 2014). While loss of estrogen has been thought of as a predominant factor in some of these disorders, reproductive changes could foretell a common underlying pathology that contributes to declining ovarian reserve and CVD risk in women.

In general, infertile men are less healthy than fertile men (Salonia *et al.*, 2009), and men with abnormal semen quality are more likely to have hypertension and heart disease. The incidence of ischemic heart disease is ~60% higher in infertile men compared to all other men (Eisenberg *et al.*, 2016a, b). Data from studies linking fertility to cardiovascular health – using fatherhood as a surrogate – also showed a positive correlation (Lawlor *et al.*, 2003). Low testosterone levels in men have been linked to greater risk of a cardiovascular event (Khaw *et al.*, 2007). Studies have shown that men with semen abnormalities also experience an earlier mortality (Jensen *et al.*, 2009; Eisenberg *et al.*, 2014).

Fertility status and cancer

While it is apparent that infertility can result from cancer or its treatment, emerging evidence demonstrates that infertility might also serve as a marker for elevated cancer risk. The specific associations are

difficult to assess, in part owing to the complexity of cancer, but the literature reveals some intriguing interrelationships. Studies of mice lacking the breast cancer genes *BRCA1* and *BRCA2*, tumor suppressors that maintain genomic integrity through repair of DNA double strand breaks, demonstrate links between infertility and breast cancer (Xu et al., 2003; Sharan et al., 2004; Hartford et al., 2016). Repair of double-stranded breaks occurs by homologous recombination, and defects in the process are a common molecular mechanism in both tumorigenesis and infertility. *BRCA1* mutant male mice undergo apoptotic elimination of spermatocytes because of a failure in double-stranded DNA repair. In oocytes, impaired spindles result in misaligned chromosomes.

Moreover, women who carry a *BRCA1* mutation have a reduced oocyte pool and produce fewer eggs compared to women with wild-type *BRCA1* (Oktay et al., 2010). However, other studies found no association between *BRCA1/BRCA2* mutations and infertility (Pal et al., 2010). It is possible that *BRCA1/BRCA2* haplo-insufficiency in germ cells might contribute to a diminished egg supply without clinically apparent infertility. In support of this, *BRCA1/BRCA2* carriers who did not undergo prophylactic surgery, chemotherapy, or radiation entered menopause three years sooner than control women (Lin et al., 2013). Thus, identifying young women with low ovarian reserve may lead to new cancer screening strategies.

The association between female fecundity and tumorigenesis is equally complex. For example, risk levels vary between those not bearing children (nulliparity) and women with infertility (those taking longer than 12 months to conceive). Nulliparity is an established risk factor for breast, ovarian and endometrial cancers, but it is unclear how this risk associates with actual infertility. However, anovulation, including that related to PCOS, has been associated with uterine cancer (Haoula et al., 2012). Endometriosis and tubal factor infertility are also associated with ovarian cancer. There are several possible biological mechanisms to explain these associations. Anovulation could increase the likelihood of breast and uterine cancers owing to increased estrogen in the presence of low progesterone levels. Endometriosis could increase risk of ovarian cancer because of genetic predisposition, the occurrence of pre-malignant atypical endometriosis, or hormonal and inflammatory factors. Tubal factors could increase risk of ovarian cancer as a result of aberrant inflammatory responses.

Multiple studies have established male infertility as a harbinger of cancer risk. The first case reports from the 1970s and 1980s suggested a link between testicular germ-cell dysfunction and a subsequent risk of testicular cancer (Skakkebaek, 1978; Berthelsen et al., 1982). Several large population-based cohort studies subsequently confirmed these findings. A 2002 study followed a cohort of 32 442 men for up to 32 years and demonstrated a 2.3 times higher risk of testis cancer in men with low sperm concentration (Jacobsen et al., 2000). Another study likewise demonstrated that men diagnosed with male factor infertility had a nearly three times higher risk of testis cancer in the years following evaluation (Walsh et al., 2009). The association between infertility and prostate cancer has been inconclusive, with studies suggesting no association, a positive association or a negative association (Ruhayel et al., 2010; Walsh et al., 2010; Eisenberg et al., 2015).

The etiology of the association between male infertility and cancer remains uncertain. Gestational exposures (i.e. testicular dysgenesis

syndrome) are a plausible cause (Skakkebaek et al., 2001, 2016). As up to 10% of the male genome is devoted to reproduction, common genetic pathways could also explain the association (Bonadona et al., 2011; Ji et al., 2012): mutations in MutS Homolog DNA mismatch repair genes including *MSH2*, *MSH4*, *MSH5* and *PMS2* have been associated with cancers and, in mice, cause varying forms of infertility including azoospermia.

Patients experiencing infertility are unique because they have frequent exposure to several factors which can affect their cancer risk/diagnosis, e.g. ovarian stimulation drugs and other infertility interventions, low parity, less use of oral contraceptives, higher social class and higher rates of cancer screening. Finally, it is important to consider pre-IVF exposures and underlying factors which may have led to the infertility itself.

Fertility status and metabolism

Historic population data indicate at least a correlational relationship between body weight – a ‘read-out’ of metabolic function – and fertility or fecundity. Over the last 100 years in the USA, the number of actual births has been rising but the birth rate has declined steeply. Since the 1980s, the prevalence of impaired fecundity (such as conception delays and pregnancy loss) also increased (http://www.cdc.gov/nchs/nsfg/key_statistics/i.htm#infertility). Concurrently, the prevalence of obesity in men and women of reproductive age has also risen (<http://www.cdc.gov/nchs/data/databriefs/db219.htm>). Although this relationship is correlative, the physiological connections that regulate metabolism and reproduction are known.

Female reproductive health is also linked to metabolic status. Energy balance is important in normal fertility, as shown by examples of increased prevalence of infertility in women with anorexia, obesity or those who exercise excessively. Women with PCOS are often both infertile and obese, and suffer from metabolic syndrome. Even lean women with PCOS often have insulin resistance, and it is possible that the molecular mechanisms of insulin resistance are the common pathway linking infertility and poor metabolic health. Women with PCOS have an elevated risk for diabetes even after adjusting for obesity. Obesity causes an inflammation-like state, which in turn affects steroidogenesis. The resulting shift in a woman’s fertility would be analogous to the shift caused by premature aging. As such, female infertility often reflects underlying metabolic imbalance.

Obesity is often associated with resistance to metabolic hormones such as insulin and leptin, which also modulate reproductive function. In addition, studies of female mammals show that changes in ovarian function disrupt metabolic homeostasis and can trigger the onset of metabolic (and other) pathologies (Della Torre et al., 2014). Some infertile men might biologically age faster than expected, leading to additional health burdens including metabolic dysfunction. Data demonstrate that one in 10 white European men presenting for primary infertility and one in eight presenting for secondary infertility have metabolic syndrome (Ventimiglia et al., 2015, 2017).

Male reproductive health declines with age, and men whose primary complaint is infertility have a higher number of comorbid conditions than those who seek medical attention for other issues. Indeed, the Charlson Comorbidity Index (CCI), a comorbidity index for predicting mortality (Charlson et al., 1987), is significantly higher in men who present to the clinic for infertility when compared to fertile men, and

fertility was a strong predictor of the relative CCI score. A higher CCI was linked to lower sperm concentration and higher FSH. These data suggest that fertility status could be a reasonable proxy for men's health (Salonia *et al.*, 2009). Some have suggested that the common link between male infertility and comorbid conditions could be accelerated aging: infertile men could have a poorer baseline of stem cells in both the germ line and somatic cell populations, and/or faster exhaustion of the stem cell populations.

The genome and infertility

Infertility affects 10–15% of couples, making it one of the most common disorders for people of reproductive age (Chandra *et al.*, 2013, 2014; Louis *et al.*, 2013; Thoma *et al.*, 2013). Over 50% of male cases are idiopathic, but many are thought to have an underlying genetic etiology. However, while mutations in over 200 genes have been shown to decrease fertility in animal models, few genetic causes of infertility have been validated in humans (Matzuk and Lamb, 2008; White *et al.*, 2013). Approximately 1000 genes, or 4% of the human genome, are involved in generating a functional sperm, and efforts to identify genetic causes for male infertility by relatively inefficient candidate gene sequencing approaches in relatively small cohorts of individuals have been unsuccessful until recently.

New multi-centered studies are now underway, including a recent study that showed copy number variations (CNVs) are enriched in infertile men compared to fertile controls men (Lopes *et al.*, 2013; Huang *et al.*, 2015). In addition, employing a quantitative approach that uses an 'interactome' to examine common linkages in comorbidity (Menche *et al.*, 2015), investigators detected overlapping relationships between male infertility and congenital abnormalities, male urogenital disease, nervous system disease, and endocrine disease. These studies provide a conceptual framework of common genetic pathways involved in fertility and overall health.

A separate study reported that 168 genes identified by genome-wide association study/online mendelian inheritance in man/differentially expressed genes analyses, also are significantly associated with male infertility (Tarin *et al.*, 2015). These genes are involved in diverse and basic cellular functions such as ribosome and proteasome pathways and regulation of metabolism, RNA degradation and translation.

Examining genetic correlations in the absence of specific gene lists could also reveal comorbidities. An atlas of genetic correlations across human diseases was recently published (Bulik-Sullivan *et al.*, 2015). Although infertility was not included in the analysis, the model can be used to compare infertility with other conditions in the future.

Discussion

Recommendations and next steps

While the etiology remains uncertain for infertility, the current body of evidence suggests four main categories for considering biological explanations: genetic factors, hormonal factors, *in utero* factors and lifestyle/health factors. These categories would be key to include across future studies to develop a comprehensive and possibly standardized look at fertility status and overall health. Several themes emerged from the workshop discussion including strategies for maximizing use of existing resources and databases, the need for additional epidemiologic studies and public health surveillance, development of strategies to frame

research so that results could ultimately influence clinical practice, and the identification of short and long-term goals and the best means to achieve them.

A number of immediate recommendations emerged. Participants agreed that the development of a common working definition of infertility is a key, pressing need and that the definition needs to include the infertile couple. A consensus conference could address this goal. In addition, detailed questions to assess fertility status for both sexes should be developed for inclusion in NHANES (National Health and Nutrition Examination Survey) and other health-focused surveys. NHANES should also consider initiating the collection of biomarkers of fertility that can be linked with behavioral data (diet, lifestyle, etc).

In the near future, researchers will need to use the data that are already available more efficiently. Existing databases could be used for secondary analysis, and, at the same time expanded by leveraging clinical cohorts, e.g. the Reproductive Medicine Network, the All of Us Program (formerly the Precision Medicine Initiative), and dbGAP. Scientific societies, such as the American Society for Reproductive Medicine and the Society for the Study of Male Reproduction, should help to support workshops on mining existing databases to allow investigators to develop consortium-type science. Additional epidemiological work is important, especially to resolve controversies in the literature. Moreover, establishing fertility along the spectrum of health will allow incorporation of reproductive health research in studies of other health disorders.

Long-term preconception cohort studies are necessary, but admittedly expensive, to identify individuals who will experience not only infertility but also other fecundity impairments such as conception delays and pregnancy loss, and their interaction with health across the lifespan. The identification of cases where infertility and co-morbid conditions are particularly severe, e.g. men with non-obstructive azoospermia at age 25 years who die from CVD by age 40 years, if available, might improve the knowledge of possible mechanistic links.

One immediate possibility is a detailed bioinformatics study of the available data that could begin to identify pathways that are involved in both reproduction and somatic diseases and disorders. It is important to note that the workshop did not address all areas of health potentially related to fertility (e.g. the immune system).

Further development of the field requires creation of new animal models which are critical to allow identification of biomarkers for infertility and for efforts to probe mechanisms that link infertility with other health conditions. For example, the US National Institutes of Health Knock Out Mouse Production and Phenotyping (KOMP2) project seeks to establish gene knockouts and phenotyping for every protein-coding gene in the mouse genome, along with tissue banking, tissue expression studies and transcriptome analysis. Although information on fertility is one of the several tiers of standard phenotyping, deep phenotyping of some strains needs to be performed to determine if infertility is associated with other health issues. Studies to date have established that a large number of knock-out strains exhibit male infertility; as might be expected fewer female infertile strains were identified. In total, 5–6% of strains show some level of infertility.

Currently, medical care is compartmentalized and specialists frequently do not know how best to treat the individual as a whole or to assess and minimize future health risks in body systems outside of their area of expertise. Reproductive medicine physicians treat patients for a short period of time before they transition to others for future care.

Going forward, it is critical to take an interdisciplinary patient care approach that would involve experts in a broad range of medical specialties in order to more fully understand the complex interrelationships between fertility and overall health. Indeed, if infertility is confirmed as an early marker of chronic disease, screening practices could be adjusted, as they are for patients with a family history of malignancy.

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Authors' roles

M.I.C., S.E.T., L.V.D., L.W., S.B.M. and M.L.E. organized the meeting. M.I.C., S.E.T., S.B.M. and M.L.E. wrote the proceedings. M.I.C., S.E.T., L.V.D., L.W., S.B.M. and M.L.E. approved the final version.

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