Published in final edited form as:

Fertil Steril. 2008 February ; 89(2 Suppl): e119–e121. doi:10.1016/j.fertnstert.2007.12.043.

Periconception Window: Advising the Pregnancy Planning Couple

Germaine M. B. Louis, PhD¹, Maureen A. Cooney, MPH¹, Courtney D. Lynch, PhD¹, and Alexis Handal, PhD¹

¹Epidemiology Branch, Division of Epidemiology, Statistics & Prevention Research, National Institute of Child Health & Human Development, 6100 Executive Blvd., Room 7B03, Rockville, MD 20852

Abstract

Objective—To discuss the importance of the periconceptional window with regard to being a critical window of exposure. To review the empirical data related to healthy periconceptional behaviors.

Design—Literature review.

Conclusion(s)—Human reproduction is a couple-dependent process. Recent literature has highlighted that the periconceptional time period is a critical window of exposure that can impact growth and development. In advising the pregnancy planning couple, it is of paramount importance that couples have knowledge of the timing of the fertile window to ensure that intercourse occurs on days with the maximum probability of pregnancy. Many women adopt healthier lifestyles while trying to conceive, often quitting smoking, eating healthier or taking vitamins. However, there is a lack of empirical data from prospective studies regarding which environmental exposures or behaviors are or are not safe. Noticeably absent are data regarding the effect of male partners' exposures or behaviors on couple fecundity and fertility. As we improve our ability to pinpoint the timing of conception, we should be able to better advise couples planning pregnancy.

Keywords

critical windows; environment; parental exposures; preconception; pregnancy planning

Introduction

Successful human reproduction and development requires completion of a series of highly interrelated and time-dependent processes involving both partners of the couple. Human reproduction is a relatively inefficient process in comparison to other species (1). This is evidenced by human reproduction's highly selective survival process that commences with the

Address all correspondence to Dr. Louis at above address.
louisg@mail.nih.gov, 301-496-6155, 301-402-2084 (fax)
cooneyma@mail.nih.gov, 301-594-9148, 301-402-2084 (fax)
lynchcd@mail.nih.gov, 301-435-6928, 301-402-2084 (fax)
handalal@mail.nih.gov, 301-435-2295, 301-402-2084 (fax)

Conflict of Interest: None of the authors have any known conflicts.

Presented on January 30, 2007 at the UCSF-CHE Summit on Environmental Challenges to Reproductive Health and Fertility.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

development of follicles and the eventual selection of a single dominant follicle for ovulation, followed by a relatively low probability of conception, implantation, and embryonic survival. Prospective pregnancy studies with preconception enrollment of women report cumulative probabilities of pregnancy at one, three and six months of trying to conceive as ranging from 38%–43%, 60%–68%, and 81%–94%, respectively (2,3).

The loss of conceptions among fecund couples, or those biologically capable of reproducing, supports the vulnerability of the human conceptus during the earliest stages of human development. As recently reviewed, the periconception window is one of the earliest critical windows for human development (4). The absence of a biomarker of human conception challenges investigators' ability to obtain empirical evidence regarding the parental determinants of human fecundity and fertility. Studies focusing on couples undergoing assisted reproductive technologies, however, offer new insight about early parental influences on the developing human organism. For example, oocyte quality has been positively associated with embryonic quality (5,6). Noticeably less research has focused on paternally mediated factors, though a positive association between sperm morphology and blastomere cleavage rate (7) has been reported as have centrosome defects and disorders of fertilization or early development (8).

The purpose of this paper is to briefly describe the critical windows of human development, assess the current research data available on parental determinants of human fecundity and fertility, and discuss the recommendations and guidelines available to the pregnancy planning couple.

Periconception Critical Window

A critical window may be defined as the time-sensitive interval during which exposures or events disrupt or interfere with the physiology of a cell, tissue or organ (9). It is a period characterized by marked cellular proliferation and development and numerous changing metabolic capabilities in the developing organism (10). Dose dependent exposures during this window may result in adverse permanent and irreversible effects. Authors have suggested the need to define both critical and sensitive periods in recognition that exposures during the latter may still affect development or result in eventual adult disease, but with reduced magnitude in comparison to exposures within critical windows (11).

We define the periconception window as the time preceding, including and immediately following human conception. This definition allows for variability in operationalizing the lower and upper bound of the window depending upon the research question. This is particularly important given the increasing evidence that *in utero* exposures may have intergenerational effects (12). For example, intrauterine growth restriction is associated with poorer ovarian development, smaller ovaries, greater anovulatory cycles and diminished responsiveness of the female to follicle stimulating hormone (13,14). Among males, intrauterine disturbances in hormonal milieu have been associated with hypospadias, cryptorchidism, diminished sperm counts, and testicular cancer collectively described as the testicular dysgenesis syndrome (15). Men with testicular cancer are reported to have diminished fecundity prior to diagnosis suggesting that impaired fecundity may be on the causal pathway to this cancer or another manifestation of the underlying defect (16). Thus, the periconception window offers researchers an ability to measure potential toxicants while assessing the epigenetic influences within the context of exogenous and endogenous factors (e.g., nutrition, environment, stress, and medications). Choice of the operational definition of the periconception window rests in part upon the study question and characteristics of the exposures and behaviors under study.

Advising the Pregnancy Planning Couple

The absence of a biomarker for human conception limits our ability to develop a body of empirical and reproducible evidence that can be utilized to develop preconception guidelines. However, clearly, it is of paramount importance that couples understand how best to time intercourse in order to achieve pregnancy. Recent evidence underscores the need to time intercourse during the six-day fertile window to maximize conception probability while considering parental ages (17–19). Investigators have found that many women do not know “their” true fertile window. In fact, only 25%–30% women have all the days of their fertile window fall between days 10–17 of their menstrual cycle which is often cited as ‘the’ fertile window (20,21).

Women desirous of pregnancy actually adopt healthy behaviors such as reducing use of cigarettes and alcoholic beverages (22,23) and increasing use of multivitamins including folic acid for the reduction of neural tube defects (24,25) as recommended in clinical and public health messages. We are unaware of any research focusing on women or couples’ behavioral intentions while attempting pregnancy with regard to preconception guidance. This may reflect a limited number of prospective pregnancy studies with preconception enrollment of women assessing lifestyle and behavioral influences on human reproduction and development (26). The best evidence we have detailing the effect of parental exposures on the conceptus and early embryo comes from these studies. Most have focused on behaviors such as cigarette smoking, alcohol and caffeine consumption, intercourse patterns, and extremes of body mass index among women trying to become pregnant.

We are unaware of papers employing quantitative methods for pooling and weighing the results of individual studies save for a few expert reviews (27,28). Suffice to say, smoking, alcohol, and caffeine consumption have been associated with diminished female fecundity as measured by a longer time to pregnancy (29–32), though often with equivocal results or of varying magnitude. In addition, at least one author has reported a negative relation between perceived stress (33) or douching practices (34) and female fecundity.

Preconception Care

A recent survey of the membership of the American College of Obstetricians and Gynecologists reported that physicians think preconception care (PCC) is important and 95% recommend it to women planning pregnancies but only 54% to sexually active women (35); however, 49% of respondents reported that patients actually seek PCC. A systematic search of the literature from 1996–2005 regarding PCC concluded the absence of current comprehensive guidelines and the lack of formal evaluation of clinical guidelines (36). However, recently, the Centers for Disease Control and Prevention released PCC guidance that focuses on the importance of accessing health care for the pregnancy planning couple (37)

Public health messages should recognize that some exposures are avoidable while others are not. Engaging in moderate physical activity and exercise is important for fecundity and general well being as is enjoying a healthy diet, maintaining a healthy weight, avoiding exposure to active and passive cigarette smoke, and avoiding consumption of alcoholic and caffeinated beverages.

Following guidelines for preparing fish meals (trimming the fat, removing or puncturing the skin, and choosing a method other than frying for cooking the fish) may also help to reduce exposure to persistent chemicals and metals. These are but a few of the many potential lifestyle or behavioral factors that may impact couple’s fecundity and/or fertility. Increasingly, investigators are recognizing the potential for long term health implications associated with intrauterine exposures. As a result, interest is arising in a life course approach to the study of

chronic diseases so that the many etiologic pathways operating over an individual's life can be considered in the context of disease etiology (11). In sum, quantifying exposures during critical windows including the periconception window may identify direct effects on the developing organism over the course of his/her lifespan and, potentially, that of future generations. As new data emerge regarding effective strategies for avoiding environmental exposures to persistent or short lived compounds, more specific advice should become available.

Summary

The absence of data on the effect of periconceptional parental exposures and human reproduction and development limits our ability to develop evidence based preconception guidelines that are responsive to the couple-dependent nature of human reproduction and development. Targeting messages tailored to both partners of the couple is an important step in developing public health campaigns promoting healthy behaviors during all critical windows of human development including the periconception interval. Ultimately, formal evaluation of such guidelines is needed along with their lasting impact on couples' behavior. While researchers strive to fill critical data gaps about the effects of the environment as globally defined on human reproduction and development, the public may do well to continue behaviors such as healthy eating, engaging in moderate exercise, and consulting clinicians when in doubt to mitigate the effects of exogenous agents not under their control. Given the evolving body of evidence supporting considerable reprogramming of embryos and fetuses in relation to *in utero* stimuli, the importance of the periconception window in relation to parental environmental exposures and behaviors cannot be understated. To this end, purposeful research is not only timely but needed so that the advice we offer couples is empirically or evidenced based.

Acknowledgements

Financial Support: This research was supported by the Intramural Research Program of the National Institute of Child Health & Human Development, National Institutes of Health.

Reference List

1. Martin RD. Human reproduction: a comparative background for medical hypotheses. *J Reprod Immunol* 2003;59(2):111–135. [PubMed: 12896817]
2. Gnoth C, Godehardt D, Godehardt E, et al. Time to pregnancy: results of the German prospective study and impact on the management of infertility. *Hum Reprod* 2003;18(9):1959–1966. [PubMed: 12923157]
3. Wang X, Chen C, Wang L, et al. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril* 2003;79(3):577–584. [PubMed: 12620443]
4. Chapin RE, Robbins WA, Schieve LA, et al. Off to a good start: the influence of pre- and periconceptional exposures, parental fertility, and nutrition on children's health. *Environ Health Perspect* 2004;112(1):69–78. [PubMed: 14698934]
5. Loutradis D, Drakakis P, Kallianidis K, et al. Oocyte morphology correlates with embryo quality and pregnancy rate after intracytoplasmic sperm injection. *Fertil Steril* 1999;72(2):240–244. [PubMed: 10438988]
6. Xia P. Intracytoplasmic sperm injection: correlation of oocyte grade based on polar body, perivitelline space and cytoplasmic inclusions with fertilization rate and embryo quality. *Hum Reprod* 1997;12(8):1750–1755. [PubMed: 9308806]
7. Salumets A, Suikkari AM, Mols T, et al. Influence of oocytes and spermatozoa on early embryonic development. *Fertil Steril* 2002;78(5):1082–1087. [PubMed: 12413998]

8. Asch R, Simerly C, Ord T, et al. The stages at which human fertilization arrests: microtubule and chromosome configurations in inseminated oocytes which failed to complete fertilization and development in humans. *Hum Reprod* 1995;10(7):1897–1906. [PubMed: 8583008]
9. Morford LL, Henck JW, Breslin WJ, et al. Hazard identification and predictability of children's health risk from animal data. *Environ Health Perspect* 2004;112(2):266–271. [PubMed: 14754582]
10. Calabrese EJ. Sex differences in susceptibility to toxic industrial chemicals. *Br J Ind Med* 1986;43(9):577–579. [PubMed: 3756106]
11. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol* 2002;31(2):285–293. [PubMed: 11980781]
12. Susiarjo M, Hassold TJ, Freeman E, et al. Bisphenol A Exposure In Utero Disrupts Early Oogenesis in the Mouse. *PLoS Genet* 2007;3(1):e5. [PubMed: 17222059]
13. Ibanez L, Valls C, Potau N, et al. Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. *J Clin Endocrinol Metab* 2000;85(10):3526–3530. [PubMed: 11061495]
14. de Bruin JP, Dorland M, Bruinse HW, et al. Fetal growth retardation as a cause of impaired ovarian development. *Early Hum Dev* 1998;51(1):39–46. [PubMed: 9570030]
15. Skakkebaek NE, Rajpert-De ME, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001;16(5):972–978. [PubMed: 11331648]
16. Baker JA, Buck GM, Vena JE, et al. Fertility patterns prior to testicular cancer diagnosis. *Cancer Causes Control* 2005;16(3):295–299. [PubMed: 15947881]
17. Dunson DB, Colombo B, Baird DD. Changes with age in the level and duration of fertility in the menstrual cycle. *Hum Reprod* 2002;17(5):1399–1403. [PubMed: 11980771]
18. Dunson DB, Bigelow JL, Colombo B. Reduced fertilization rates in older men when cervical mucus is suboptimal. *Obstet Gynecol* 2005;105(4):788–793. [PubMed: 15802406]
19. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med* 1995;333(23):1517–1521. [PubMed: 7477165]
20. Fehring RJ, Schneider M, Raviele K. Variability in the phases of the menstrual cycle. *J Obstet Gynecol Neonatal Nurs* 2006;35(3):376–384.
21. Wilcox AJ, Dunson D, Baird DD. The timing of the "fertile window" in the menstrual cycle: day specific estimates from a prospective study. *BMJ* 2000;321(7271):1259–1262. [PubMed: 11082086]
22. Ebrahim SH, Decoufle P, Palakathodi AS. Combined tobacco and alcohol use by pregnant and reproductive-aged women in the United States. *Obstet Gynecol* 2000;96(5 Pt 1):767–771. [PubMed: 11042316]
23. Eriksson KM, Salvesen KA, Haug K, et al. Smoking habits among pregnant women in a Norwegian county 1987–1994. *Acta Obstet Gynecol Scand* 1996;75(4):355–359. [PubMed: 8638456]
24. House JD, March SB, Ratnam MS, et al. Improvements in the status of folate and cobalamin in pregnant Newfoundland women are consistent with observed reductions in the incidence of neural tube defects. *Can J Public Health* 2006;97(2):132–135. [PubMed: 16620001]
25. Thompson SJ, Torres ME, Stevenson RE, et al. Periconceptional multivitamin folic acid use, dietary folate, total folate and risk of neural tube defects in South Carolina. *Ann Epidemiol* 2003;13(6):412–418. [PubMed: 12875798]
26. Buck GM, Lynch CD, Stanford JB, et al. Prospective pregnancy study designs for assessing reproductive and developmental toxicants. *Environ Health Perspect* 2004;112(1):79–86. [PubMed: 14698935]
27. Augood C, Duckitt K, Templeton AA. Smoking and female infertility: a systematic review and meta-analysis. *Hum Reprod* 1998;13(6):1532–1539. [PubMed: 9688387]
28. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. *Fertil Steril* 2004;81(2):384–392. [PubMed: 14967378]
29. Jensen TK, Hjollund NH, Henriksen TB, et al. Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. *BMJ* 1998;317(7157):505–510. [PubMed: 9712595]

30. Jensen TK, Henriksen TB, Hjollund NH, et al. Caffeine intake and fecundability: a follow-up study among 430 Danish couples planning their first pregnancy. *Reprod Toxicol* 1998;12(3):289–295. [PubMed: 9628552]
31. Zaadstra BM, Seidell JC, Van Noord PA, et al. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. *BMJ* 1993;306(6876):484–487. [PubMed: 8448457]
32. Baird DD, Wilcox AJ. Cigarette smoking associated with delayed conception. *JAMA* 1985;253(20):2979–2983. [PubMed: 3999259]
33. Sanders KA, Bruce NW. A prospective study of psychosocial stress and fertility in women. *Hum Reprod* 1997;12(10):2324–2329. [PubMed: 9402304]
34. Baird DD, Weinberg CR, Voigt LF, et al. Vaginal douching and reduced fertility. *Am J Public Health* 1996;86(6):844–850. [PubMed: 8659660]
35. Morgan MA, Hawks D, Zinberg S, et al. What obstetrician-gynecologists think of preconception care. *Matern Child Health J* 2006;10(5 Suppl):59–65.
36. Curtis M, Abelman S, Schulkin J, et al. Do we practice what we preach? A review of actual clinical practice with regards to preconception care guidelines. *Matern Child Health J* 2006;10(5 Suppl):53–58.
37. Johnson K, Posner SF, Biermann J, et al. Recommendations to improve preconception health and health care--United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep* 2006;55(RR6):1–23. [PubMed: 16617292]