Reflections on Future Research in Adolescent Reproductive Health

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A group of basic scientists, clinicians, clinical investigators, psychologists, patient advocacy groups, and representatives from professional societies and governmental agencies met at the National Institutes of Health in October, 2007 with the long-term goal of having the menstrual cycle accepted and understood as a marker of general health in adolescent girls. An equally important goal was to develop a research agenda for this area of investigation. This chapter comprises the highlights of discussions throughout that meeting, with an emphasis on ideas generated during a final session led by an internationally renowned physician–scientist, in which reports from four breakout groups were presented. The specific goal assigned to each group was to develop an agenda that would set the stage for how research should be conducted over the next 100 years, and to identify the pressing research questions that should be addressed related to the menstrual cycle and adolescent health. The four research areas represented in discussion groups included: emotional health; genetics; metabolism and reproduction; and the promotion of conduct of clinical research. Insights are also provided by five clinical investigators, including two outside experts, on topics of priority for a research agenda in the area of adolescent reproductive health, as well as how the research itself should be conducted.

Key words: **research; adolescents; reproductive health; menstrual cycle**

Background

Individuals from diverse backgrounds—including clinicians, clinical investigators, basic scientists, psychologists, patient advocacy groups, and representatives from professional societies and governmental agencies—assembled in October 2007 for a meeting entitled "The Menstrual Cycle and Adolsecent Health" convened by the NIH to discuss issues relevant to this important, but sometimes overlooked field. An agenda for research was also explored that aimed at identifying the topics that should have research priority for the next century. A goal of the meeting was also to devise ways to have the menstrual cycle accepted and valued as a *vital sign* by providers who care for adolescent girls and young women.[1,2] Clinical and basic scientists gave presentations that reviewed key topics in this area, with a plan to identify gaps in knowledge that would assist in formulating a research agenda. Throughout the meeting, attendees remarked that the *approaches* to carrying out research are as important as the *topics* to be investigated. This chapter reviews the final discussion, held on the concluding day of the meeting, and it is hoped that it will serve as a manifesto

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highlighting the critical needs for additional research related to the menstrual cycle and adolescent health.

Initial Insights: Reflections on Fuller Albright and Patient-Oriented Research[g]

The summarizing chapter of this *Annals* volume should reflect a *dream*—that is, it should capture the *ideal* research agenda for the next 100 years in the area of adolescent reproductive health, and specifically, as it relates to studying the menstrual cycle and its applications to adolescent health and disease. Many factors require consideration as we ponder the kind of research that should begin to take place in this vital area in the next century. In learning some of the many lessons about clinical research and how this scientific effort should be approached, we would do well to consider the life and practice of Dr. Fuller Albright, one of the most influential thinkers and medical scientists of our time.

First, we need to acknowledge the expanding knowledge in the area of genomics and our enduring fascination with the link between genotype and phenotype. However, having these powerful tools in hand, we need to consider our "genetic citizenship"—that is, the degree to which we are able to collaborate with one another in a fruitful exchange of ideas. This will determine how well we will ultimately be able to deliver answers to our patients. This type of collaboration aims at understanding the underlying pathophysiology of a disease in order to affect its optimal treatment. Although we have some information available for our use, striking gaps in our knowledge still remain. For example, we have made significant gains in understanding the varying presentation of young women with premature ovarian failure (also known as "premature menopause," or more accurately, as "primary ovarian insufficiency").[3,4] However, we understand relatively little about how a genetic predisposition ultimately leads to alterations of ovarian function. An example is carriers of the Fragile X mental retardation 1 (FMR1) premutation, who have a 20–30-fold increased risk of developing primary ovarian insufficiency. The link between the predisposing gene (e.g., FMR1) and impaired ovarian function deserves further study. Ultimately, in any type of biomedical research aimed at improving health, the patient must be the "substrate" for investigation. The Greek word *pathos* means "suffering." Our future research has to be driven to meet the needs of the *sufferers* in our society, and a healthy respect for the *pathos* associated with disease.

Dr. James Wyngaarten, director of the NIH from 1982–1989, wrote an article in 1981 entitled "The Clinical Investigator as an Endangered Species."[5] In 1974, close to the conclusion of the Vietnam War, there was a dramatic decrease in the number of individuals who held M.D. or combined M.D./Ph.D. degrees who applied for NIH funding to carry out biomedical research. These statistics were explained by fewer individuals choosing to pursue careers in biomedical research as the war was ending. In 1992, several years later, Edward H. Aherns, Jr., Emeritus Professor at Rockefeller University, wrote a book entitled, *The Crisis in Clinical Research.*[6] He described the profound shift in emphasis from patient-oriented research to research at the cellular and molecular level. Ahrens argued that changes needed to be made in the training of clinical investigators and in their funding requirements, and that new working partnerships between clinically skilled M.D.s and technically trained Ph.D.s were urgently needed to restore patient-oriented research to full productivity. He felt that a rebalancing should occur to assure that quality research resulted. To this day, there continue to be concerns that clinicians and scientists are operating from mutually exclusive positions, and that for clinicians, scholarship (scholarly reviews, teaching, etc.) can become a substitute for science. Both scholarship and science are important, but they have a different focus and mission.

Dr. Fuller Albright in his book, *Uncharted Seas*, had important insights into what features best characterize an outstanding clinical investigator.[7] He wrote about this type of investigator as "a physician with a scientific habit of mind." Albright concluded that this individual was equally comfortable in both the laboratory and on the ward. Another classic quote from that book is that "Many people see well, but neglect to look."[7] This description would *not* describe the astute clinical investigator who is constantly on guard for any information that might provide a clue to help a suffering patient. Dr. Albright exhibited unprecedented devotion to his students and colleagues, and a relentless pursuit of knowledge. Even when severely afflicted by Parkinson's disease, he continued to hold rounds with his students, residents, and Endocrine Fellows, who took copious notes for him while he continued to make important clinical observations, but was no longer able to hold his hand steady to write.

Translational research involves multidisciplinary efforts to bring about the most substantial biomedical

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[g] This portion of the paper was prepared and reported by D. Lynn Loriaux.

advances over the next 100 years. There should be constant communication and dissemination of knowledge between the basic scientist at the laboratory bench, and the clinician or clinical investigator at the patient's bedside. Work at the bench must be informed constantly by what is taking place at the bedside. It has been questioned as to whether the current system of grant evaluation renders the most benefit to physician–scientists or their patients. Perhaps the NIH or foundations should fund a person rather than a project? An example would be the Howard Hughes Foundation Program, which grants stipends to individual scientists, each an outstanding principal investigator with a track record of success, to carry out work in a given area over a several-year period. This funding then frees the scientist to put creative effort towards his or her research, rather than having to spend countless hours preparing multiple grant applications to fund the efforts of the laboratory. This approach will require a process that will be able to identify and support the future "Fuller Albrights" relatively early in their careers.

Disease Research: Knowledge, Value and Innovation[h]

Managing Innovation

In the effort to understand the underlying pathophysiology of or to discover a cure for a specific disease, specialists from diverse fields would ideally be brought together so that their talents, expertise, and ideas can be mixed. A "creative abrasion" would then result, which yields divergent, deep reservoirs of knowledge, but equally allows for diverse cognitive and communication styles to be juxtaposed.[8] As Dorothy Leonard-Barton said, "Innovation occurs at the boundary between mind sets." Biomedical research is highly competitive. Tension can arise with issues related to intellectual property and authorship and, if they are not managed skillfully, may handicap collaborative efforts. Positive outcomes that can result from the intersection of differing styles include a consortium or alliance. Negative outcomes include predatory competition and efforts that violate anti-trust issues.

A research consortium can provide the proper structure for disease research. The proper structure shifts efforts towards knowledge creation, and away from resource- and information-hoarding. An example would be a genetic disease research consortium. Patients with a given disease provide the focus, and a partnering with patients becomes the model. The National Fragile X Foundation illustrates these features, with disease researchers and their patients learning from each other, making it easy to work together, and sharing the results of their efforts. The Internet is also changing the way that patients and investigators interact with one another, inducing self-organizing behavior, aiding in information flow, and moving power to patient advocacy groups which may aid a consortium. However, this technology can also propagate misinformation. People and systems will self-organize when three vital ingredients are present: a higher common purpose, a willingness to work together, and a level of personal mastery and maturity.[9] According to Thomas A. Stewart, "Intellectual capital is the sum of everything everybody in a company knows that gives it a competitive edge."[10] It becomes clear that partnering increases intellectual power.

The organization of a disease research consortia is multi-leveled. Patients and their families provide the focus, the common shared goal of defeating a disease that drives the effort. They also provide the reason for unity. Disease groups will eventually coalesce into a common research system. Consortia will collect, store, and distribute accurate clinical data on patients with specific diseases, and enable the collection of high-quality data, such as DNA and serum samples. The core sources will be patient-led groups, and DNA and data storage facilities. Other consortia members include physician researchers, molecular geneticists, basic scientists, and individuals from pharmaceutical and biotechnical industries, academic institutions, and the NIH.

Knowledge

Creating a genetic map and finding genes creates *information*, but not knowledge. Data are a set of discrete, objective facts (e.g., a sequence of DNA). Information is data organized to convey a message (e.g., a gene). *Knowledge* is *information in context*, a fluid mix of framed experience, values, expert insight, and intuition (e.g., information utilized to understand and treat a disease). Knowledge exists at multiple levels, including the individual, the group, the organization, and inter-organizational groups. In the collaborative research effort to approach a disease, examples of individuals who may work together include patients, physicians, and basic scientists. Groups include patient support groups and research consortia. Organizational efforts include repository facilities, the pharmaceutical and biotechnical industries, academic institutions, and the NIH. Ideally, inter-organizational research endeavors would occur in which individuals of varying and complementary backgrounds collaborate for

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[h] This section of the paper was prepared by Dr. Lawrence M. Nelson.

the common good. The most innovative projects will bring individuals together from different fields. Knowledge permits action, and in biomedical research, this means knowing how to prevent, detect, or treat disease.

Value

In disease research, efforts should focus on the needs of patients in order to create the greatest value. The research then stems from what the patients need. A research team must develop and nurture the competencies needed for innovation. Ultimately, the research team must translate the knowledge created by these competencies into action for patients. The goal is to create knowledge that is of value to patients.

Insights from Two Outside Experts: Grumbach and Rogol

Remarks of Dr. Melvin Grumbach

To carry out disease research effectively, one must organize task forces (study groups) using a multidisciplinary approach, including pediatric endocrinologists, adolescent health experts, reproductive endocrinologists, behaviorists, neuroscientists (including neuroendocrinologists), experts on evolutionary and life-history theory, experts on prenatal, perinatal, and infancy events that influence disease and disability in later (adult) life, systems biologists, experts in development of patient databases and "biobanks," and experts in "omics" (genomics, proteomics, metabolomics, pharmacogenomics), population geneticists (including experts in quantitative trait loci, and biomarkers), and economists. Knowledge has expanded so dramatically over recent years that it will take a well-organized team of diverse individuals to solve the most complex of medical problems.

Advances continue in genetic research and diagnostic possibilities exist that were never available before. However, we must ask ourselves the question, "How can we best prepare ourselves for the "thousand dollar genome"—the time when genomic sequencing becomes commonplace, the era of "personalized medicine" and "personal genomics"? Within this new framework, what can we learn about puberty and the menstrual cycle?

The existence of the electronic medical record (EMR), which will have an enormous amount of up-to-the-minute databases, will have important implications for patient-oriented research. The EMR promises to revolutionize data collection and management for clinical research and epidemiologic studies, including issues related to puberty and the menstrual cycle. It also provides a method of accumulating ongoing follow-up data.

Research areas of priority over the next 100 years include the following areas noted by Dr. Grumbach:

- "Human-life history," including Gluckman and Hanson's predictive adaptive response (PAR),[11] and the evolution of human maturation, must be taken into account. More specifically, research in this area would include an in-depth, inclusive examination of factors influencing the age of menarche (including prenatal and postnatal influences on timing of menarche).[12]
- An important long-term goal is to understand the molecular mechanisms that drive the cellular processes that result in "puberty."
- There must be greater understanding of the interaction between the brain and both the reproductive endocrine system and growth hormone cascade. Gaps in knowledge still exist regarding the organizational effects of brain peptides on sex hormones and their receptors (e.g., oxytocin and its effect on expression of estrogen receptors in the brain).
- The relationship between stress hormones, behavior, and puberty must be better understood.
- We must learn how receptors in brain cells and their ligands are associated with pubertal maturation (e.g., GPR54 [a G protein–coupled receptor] and its ligand, kisspeptin, and genes expressing and regulating this system). Equally important is an understanding of the role of neuroexcitatory amino acids (e.g., glutamate), neuroinhibitory neurotransmitters (e.g., GABA), and growth factors on pubertal maturation. For example, inactivating mutations of GPR54 result in autosomal recessive hypogonadotropic hypogonadism.[13] In contrast, a polymorphism in the GPR54 gene appears to be correlated with precocious puberty in some cases, likely as a result of changes in expression of the receptor.[14]
- The relationship between hormones, bone maturation, and epiphyseal fusion must be elucidated, especially as related to mechanisms (systems biology). The exact role of vitamin D, calcium intake, parathyroid hormone, and calcitonin, among other variables (exercise, skeletal loading), is still unclear with respect to both bone accretion and growth-plate biology.
- Research should be commenced to examine more precisely the relationship between puberty and bone health. We need to improve methods for measuring bone deposition and bone

resorption, and measuring bone mineral density (including both cortical and trabecular bone) in the growing child and adolescent. We are currently limited by shortcomings in our measurement tools to evaluate various aspects of bone density and skeletal health. It is important to learn whether there is an increased fracture risk *in adolescents* with delayed adolescence, hypogonadism, and anorexia nervosa. Longitudinal studies that document whether the risk of osteoporosis and fracture is increased in these patients would also be informative and could help in the formulation of health guidelines and policy.

- Polycystic ovary syndrome (PCOS) is a common syndrome among adolescent girls and is deserving of continued attention and research. The relation of prenatal events to the development of this disorder is unclear. The role of obesity and abdominal adiposity, insulin resistance, and dyslipidemia in affected adolescents and young women should also be examined.
- An important area to address is the improvement of serum assays and other measurement tools, the lack of which currently handicaps both the clinician and clinical investigator. Better standardized, more precise, sensitive, and highly specific methods need to be developed for measuring low concentration levels of estradiol (and testosterone) in plasma of children and adolescents. Many of the present commercial kits and assay platforms are exceedingly inaccurate and expensive.
- The new powerful tools available to investigate the molecular biology and genetics of spermatogenesis and ova maturation will have important implications for health care.
- The relationship between circulating sex hormones and risk-taking behaviors in adolescents deserves further study.

Remarks of Dr. Alan Rogol

Many of the same areas were identified by both Drs. Rogol and Grumbach as research topics of priority. Many of Dr. Rogol's reflections relate to areas that can be classified as representing the biosocial sphere of adolescents. An important recent position statement on the "female athlete triad" made by the American College of Sports Medicine reviews the energy and stress aspects of pubertal maturation, bone, and the menstrual cycle.[15] The triad encompasses disordered eating, amenorrhea, and osteoporosis in the young female athlete. This statement is an important one for the field of adolescent reproductive health. A better understanding of how energy deficits mediate hormonal abnormalities, ultimately responsible for skeletal deficits and other problems, will represent a significant advance in the field.

A multidisciplinary team will be needed to address the complex research agenda of the next 100 years. In addition to members of the team identified by Dr. Grumbach, other invaluable team members would include auxologists and population biologists. The perspective of auxologists on work biology and fertility for a *population* has relevance to the study of the menstrual cycle. Psychosocial stress, in addition to energy availability, has direct relevance to maturation and an understanding of the etiology of secondary amenorrhea. The following is another list of research areas of priority:

Research areas of priority over the next 100 years include the following areas noted by Dr. Rogol:

- Great emphasis should be placed on the importance of the effects of human-life history on both development and potential alterations of the menstrual cycle. Gluckman and Hanson's predictive adaptive response (PAR) is important to consider in delineating how stress may alter active biological processes (e.g., the menstrual cycle) in a young woman.[11] An understanding of the link between stress hormones and both behavior and pubertal development would be an important part of this general goal.
- The prenatal condition has a strong relationship to puberty including early (and rapid) pubertal development. Understanding this mechanism would not only help these individuals, but would also encompass the problems of insulin resistance and hyperandrogenemia. An example of collaborative efforts that lead to multidisciplinary collaborative work and understanding of a problem is the recent consensus conference and statement organized by international societies of pediatric endocrinology and the Growth Hormone Research Society.[16]
- Increasing information is available regarding the relation between receptors in brain cells and the timing of puberty. An understanding of the known factors is needed and information about other factors (up- or downstream) must be sought.
- Bone health is an extremely important concept to consider in the adolescent, and in particular, the relationship of bone density and fracture risk to puberty and the menstrual cycle. Osteoporosis

is not just a disease of older women; in reality, it is a preventable disease of prepubertal children. There are data that show an increased risk of fractures that occur around the timing of the growth spurt in girls and boys.[17] There is a surprising lack of uniform recommendations in this area as related to nutrition and exercise with respect to bone health. There is still work to do to understand the relation between calcium and vitamin D intake (both dose and duration), and activity and the eventual development of peak bone mass. Research in this area would yield information that makes possible the formulation of pediatric nutrition and exercise guidelines, with the final goal of optimal bone health.

- The polycystic ovary syndrome (PCOS) is a common problem that represents a multifaceted disorder with many long-term health sequelae. An emphasis should be placed on finding the root causes of insulin resistance, given that it is the mechanism likely responsible for the disordered puberty and abnormalities in menstrual cyclicity seen in some small for gestational age (SGA) children, and especially in those who are obese. Five to 7% of women have PCOS[18] and many more exhibit insulin resistance,[19,20] and these teenagers and young women are at high risk for the development of type 2 diabetes mellitus.[18–20] Therefore, an emphasis should be placed on understanding the link between insulin resistance and the function of the hypothalamic-pituitary-gonadal (HPG) axis, as this problem affects not only adolescents, but is also a major public health problem of reproductive-age women.
- An important priority for any investigators in the area of reproductive health is to develop accurate and sensitive assays to measure sex hormones. A number of investigators are working on biological assays that measure all androgen receptor-stimulating (and -inhibiting) compounds and similarly for the estrogen receptor. In addition, better gas chromatography/mass spectrometry (GC/MS) assays are being developed for a specific androgen (e.g., testosterone) and estrogen (e.g., estradiol). Depending on the interest of a clinical investigator, one could focus on either set of assays.
- The future research agenda should integrate physical exercise more than has been the case. Population biologists often focus on the work product of malnutrition that may be stunting the growth of workers, making them poorer "machines" to produce work as adults. Similar points, including energy availability and physical work, are important to consider in understanding pubertal development and the menstrual cycle (how many babies do they have?) and the "quality" of the work (with reference to bone mineral accrual and attainment of the highest possible peak bone mass).
- There are data about the timing of menarche with relationship to birth order and mother's age of menarche.[21] Stress aspects, as noted previously, are likely have some relevance to understanding these processes.
- The genome will be a powerful research tool, especially if one can obtain it relatively inexpensively. However, many of the single-gene difficulties are already known or will be relatively easily found. It will be important to consider gene–gene interactions and their impact on a biological outcome (e.g., height). Bioinformatics and computing power will be key issues. This is not to suggest that the 10-year view of the reproductive cycle needs *specific* bioinformatics, just that there should be individuals evaluating the newer aspects of bioinformatics to see what may be useful in the biological studies that have been suggested.
- Research on endocrine disruptors will be important over the next 100 years as these are real (not theoretical) problems in the animal and human world.[22,23] They will likely affect the number of species that thrive and the population biology of both men and women (and the pathway—adolescent development—by which they get there). This issue will be one to consider in the development of new assays, as well as interactions with the genome. It is suspected that those with "different" detoxifying pathways would react to environmental disruptors along a spectrum, which makes their identification and understanding of biological effects more complex.

Summary of Discussion Groups

Four breakout groups were assembled from among the meeting attendees. The specific goal assigned to each group, as it was to the outside experts, was to also suggest an agenda that would set the stage for how research should be conducted over the next 100 years, and to identify the pressing research questions that should be addressed as they relate to the menstrual cycle and adolescent health. The four research areas represented in the discussion groups included: (1) emotional health; (2) metabolism and reproduction; (3) genetics; and (4) the conduct of clinical research.

Emotional Health

A number of important objectives were generated by the emotional health research group. The ultimate goal in this area is that girls and young women have a strong sense of well-being. The first objective identified was to understand the perceptions of the menstrual cycle by girls and their families within a cultural context. Specifically, how do these perceptions affect their sexual behaviors, contraceptive choices, nutritional choices, and physical activity? A biomedical outcome that would be affected by nutrition and activity choices is weight. A second objective is to understand how girls with menstrual abnormalities and their families make health care decisions. This objective includes exploring how they seek health care, adhere to treatment, and manage the emotional adjustment of being diagnosed with a health problem. The last objective identified by the group was determining the psychosocial needs of girls with chronic medical conditions and their families with regard to making menstrual management decisions, sexuality, and future reproductive potential.

This group also discussed a number of other topics. They suggested that the concepts of emotional health be included in large, representative studies of adolescents (e.g., National Health and Nutrition Examination Survey [NHANES], Add Health, etc.) Questions related to emotional and reproductive health could also be added to questionnaires for ongoing studies that currently lack these components. The Centers for Disease Control and Prevention should be encouraged to consider increasing preventive efforts in the area of reproductive health and the menstrual cycle. Many current research studies focus on biomedical outcomes. Qualitative research in the area of emotional health related to the menstrual cycle would likely more accurately capture both the current understanding and impact of past experiences of adolescent girls and their families. Lastly, complementary to what was discussed by one of the other subgroups, longitudinal studies need to be designed that specifically examine the relationship between biological outcomes and psychosocial influences surrounding puberty and the menstrual cycle.

The most significant obstacle identified by the group—one that greatly hinders research in this area—is the inability of investigators to frame and ask the appropriate questions. For example, the corpus of questions currently posed may contain unknown biases or be otherwise flawed. Investigators are often unaware of this and so errors continue to be propagated. Or in some cases many investigators do not consider the cultural differences that may be present as a question is asked. Two solutions to this problem were suggested. First, standardized questionnaires could be developed that could be used by both national and international representative (or population) studies, as well as by disease-specific networks. Second, a standardized set of core questions could be developed for both hypothesis-generating and hypothesis-confirming studies.

Metabolic and Reproductive Research

This group proposed the need for a Study of Puberty across the Nation (SPAN) that would be similar to the Study of Women's Health across the Nation (SWAN) Study, a multiethnic study of menopause. This prospective multicenter and multiethnic study would enroll children, adolescents, and young adults, aged 9–24 years, in order to provide prospective data on several health outcomes. A priority set by this group was the important relationship that exists between puberty and bone mineral accretion. A goal of the study would be to obtain information related to several health outcomes or biological processes (e.g., pubertal maturation), each a variable known to affect bone density, a primary outcome of the study. It was also acknowledged that osteoporosis is considered by many experts to be a "pediatric disease" in onset, one that is very important to prevent, expecially in view of the risk factors for hip fracture among other skeletal outcomes suspected to emanate from factors during the childhood and adolescent years.[24] Information would be obtained in a variety of areas, providing a rich, multifaceted database. The types of data collected would include anthropometric information, dual-energy X-ray absorptiometry (DXA, bone density and body composition), peripheral quantitative computed tomography (pQCT) (bone density, geometry, and strength), bone turnover markers, menarche and the menstrual cycle, banked DNA, selected disease markers, and Tanner pubertal staging. It was acknowledged that there is currently a paucity of data relevant to what constitutes the normal range for several of these variables. Therefore, a primary contribution of the study would be the collection of reference data for bone density, bone turnover markers, and body composition, among other endpoints, in normally growing and developing children and adolescents.

The group stated that a large final sample size would be needed to provide the most accurate normative data and to draw accurate conclusions. Therefore, the multi-center approach would enable clinical investigators at each site to collect data in a uniform way to permit the findings to be pooled. A limitation of individual investigator-initiated projects is that the small sample size from one site can limit the generalizability of the findings. In addition, if different assays, DXA scanners, or methods for assessing pubertal status are used, the results from multiple centers cannot be combined. The SPAN Study, in which outcomes and uniform measurement tools would be identified *a priori* and collaborations developed before data are collected, would circumvent many of the current problems that have hampered the establishment of reference data. Another obstacle to the collection of these important data is funding. Therefore, it is hoped that an application to the NIH could be submitted that includes multiple principal investigators (PIs) to carry out the research effort. Allowing a single application to have multiple PIs was noted as a more feasible way of enabling the academic clinical investigator, who has to balance the competing demands of clinical research, patient care, and teaching, to carry out this work in a timely way.

Genetic Research

This group stated that in setting priorities for studying genetics in the area of adolescent reproductive health, one should be mindful of those with the broadest appeal and clinical application. It was acknowledged that there is still much to understand regarding the biology underlying oogenesis, the first step in the complex process of reproduction. Premature ovarian insufficiency (POI) was identified as a problem for which a surprising amount is still unknown. It was recommended that a whole-genome association approach be used in an effort to understand the causes and predisposition to POI, including the enrollment of ethnic-specific controls to identify POI genes. The whole-genome approach can be especially helpful if a clear marker has been identified, as is the case in young women with POI. Specific diseases known to cause alterations in ovarian function (e.g., Turner syndrome, galactosemia, *FMR1* premutation, etc). may be used as models to determine the relative contribution of prenatal and postnatal variables to the ultimate clinical phenotype. One particularly appealing model would be longitudinal population-based studies of women who possess a premutation in the *FMR1* gene, a single-gene cause of altered ovarian function. A prospective research model could be organized that would assess the incidence of altered ovarian function in this population, future effects of disease, and the pathologic mechanisms underlying the associated abnormal ovarian function. The primary approach here would be bedside to bench, and then bench back to bedside.

Promoting Conduct of Clinical Research

Throughout the meeting, the concern was raised by numerous individuals from varying disciplines that current regulations all too often handicap the efforts of investigators. Therefore, one group discussed ways to facilitate translational research in adolescent health (from bedside-to-bench and back), including the study of gonadal function and its impact on reproductive, bone, and psychological health and well-being.

The problems recognized included the prolonged and inefficient review process that is required for each individual research protocol including those of the General Clinical Research Center (GCRC), Institutional Review Board (IRB), institutional/legal-NIH-regulatory, Office for Human Research Protections (OHRP), Food and Drug Administration (FDA) applications and ultimate approval; a lack of unification of scientific and IRB review, which delays the process; lack of direct communication between investigators and their local IRB, which prolongs final approval because of miscommunications that are generated; guidelines for minimal risk that are not clearly defined; and the existence of excess bureaucracy in the review of protocols and consent forms (HIPPA). Other problems cited include a lack of recognition that the adolescent level of risk is unique (e.g., pregnancy potential) and not age-related (i.e., stage-related). Lastly, debt accrual by potential clinical investigators often forces them to enter clinical practice over academic research because of financial concerns. The frustrations generated by excessive regulatory issues can discourage a young scientist who is considering a career in clinical investigation.

Solutions to recognized problems were also generated and discussed. Proposed recommendations included that the Secretary's Advisory Committee on Human Research Protections (SACHRP) direct OHRP to give IRBs clear guidance on minimal risk, thereby streamlining the research review process in ongoing collaboration with the research community. More specific recommendations included that the NIH develop a flexible, speedy process of funding translational research teams directly. Professional societies should also develop guidelines and consumer education materials to promote translational research. General suggestions identified by the group included that investigators be encouraged to interact directly with their local IRB. It was felt that this interaction would facilitate communication and avoid needless delays in the approval process. Attempts should be made to avoid the multiple obstacles that exist for investigators as they try to enroll healthy control subjects to carry out a well-designed clinical trial. Lastly, it was recognized that promoting adolescent menstrual cycle research is "preventive medicine" for adult disorders, therefore making it a priority area as research agendas are being set.

Incentives for Expanding Numbers of Clinical Investigators

There is a need to expand the research work force in the area of the menstrual cycle and adolescent reproductive health. A suggestion for increasing numbers of clinician–researchers is to have the cost of malpractice insurance covered by a governmental program set up for this purpose. Attendees at the meeting cited the cost of insurance as a difficult impediment for physicians who must spend half or more of their time on what may be viewed as less lucrative research. There was also discussion around the NIH and other federal agencies considering the projected productivity of an outstanding individual scientist, rather than the current system of assessing the scientific merit of individual projects. Dr. Loriaux referred in his keynote address to a model in which the NIH "funds the person, not the project." The current system hinders creative effort and slows the advancement of current research as an extraordinary amount of time is spent by a PI in the preparation of grant applications to keep a laboratory or research group funded. The NIH Loan Repayment Program (LRP) has been met with tremendous success as young physician–scientists are able to pursue patient-oriented research in exchange for loan forgiveness. This type of program will enable young scientists to make decisions driven by their interests and personal commitments to a cause, rather than having to be burdened by the financial constraints generated by college and medical school expenses.

Summary

Research in adolescent reproductive health, and specifically, related to the menstrual cycle should be a high priority for the NIH and other funding agencies. Many disease processes stem from problems arising during the adolescent years. Absence of or presence of irregular menses can be a clue to the presence of these problems, which, if identified early and treated, can prevent more serious long-term disorders. Examples discussed include type 2 diabetes in an adolescent with PCOS and later osteoporosis in a teenage adolescent athlete with amenorrhea. Both the specific topics that make up the research agenda and the process of how the research is carried out are equally important considerations. Research consortia centered on a specific disease represent a feasible structure to carry out work both effectively and in a timely way. Involving the work of patients and their families with that of both clinical and basic investigators results in research that will have the broadest applications. There remain concerns, however, that the clinical investigator is an endangered species. Several thoughtful incentives have been suggested to nurture young investigators as they make long-term career decisions. This must become a priority for these young scientists will become the next generation to take up the banner of investigation in the area of the menstrual cycle and adolescent health.

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Conflicts of Interest

The authors declare no conflicts of interest.

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