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Prolapse Consensus Conference Summary Report

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Abstract

Objectives: The 2016 American Urogynecologic Society Prolapse Consensus Conference brought together thought leaders in the field of pelvic organ prolapse (POP). The goal was to identify critical areas of need for future research. This manuscript summarizes the findings.

Methods: Prior to the conference, five major focus areas were identified. Focus areas were explored over the 2-day conference. Clinicians, clinical and basic science researchers, representatives from government agencies, industry, patient advocacy groups, and the public convened to identify the major gaps in knowledge in each of these focus areas.

Results: The five major topics were: 1) Mechanistic research on pelvic supportive structures and how these are altered with pregnancy, delivery, and aging; 2) Novel prostheses or implants that address pathophysiology and provide mechanical support; 3) Large-scale community-based research; 4) Clinical trials to optimize outcomes after POP surgery; and 5) Evidence-based quality measures for POP outcomes. Key recommendations were made for each topic.

Conclusions: Critical gaps in our knowledge were identified. These limit scientific discovery across all 5 topic areas. Further scientific progress would be advanced by: 1) developing a standardized group of POP outcomes and quality measures for large trials and community-based research; 2) the creation of specimen biorepositories that are integrated with robust clinical data; and 3) the development of collaborative teams with expertise from a variety of disciplines, convened to tackle our most challenging and complex scientific questions.

Keywords

consensus report; AUGS; prolapse research

Introduction

The American Urogynecologic Society (AUGS) supports the advancement of knowledge regarding all aspects of female pelvic medicine, the dissemination of related scientific discoveries, and the training of health care professionals and researchers in this field. In this spirit, the 2016 AUGS Prolapse Consensus Conference brought together thought leaders in the field, including clinicians, clinical and basic science researchers, representatives from government agencies, industry, patient advocacy groups, and the public. The goal of the conference was to identify critical areas of need for future research.

Prior to the conference, the AUGS scientific community completed a web-based survery to identify the highest priority research questions pertaining to pathophysiology and treatments of POP. A total of 15 separate items were evaluated using a modified Delphi approach [1] and ultimately five major focus areas were identified:

1. Mechanistic research on pelvic supportive structures and how these are altered with pregnancy, delivery, and aging
2. Novel prostheses or implants that address pathophysiology and provide mechanical support
3. Large-scale community-based research
4. Clinical trials to optimize outcomes after POP surgery
5. Evidence-based quality measures for POP outcomes

Over a 2-day consensus meeting, these five topic areas were explored. The goal was to combine scientific, industry, funding agency, and patient perspectives to identify the major gaps in knowledge in each of these topic areas. Here we summarize the results of this interactive conference.

I. Mechanistic Research on Pelvic Supportive Structures and How These are Altered with Pregnancy, Delivery, and Aging

The anatomical failure rate after POP surgery is as high as 25%, even when “gold standard” surgical procedures are employed.[2] This suggests great opportunity for improvement: simply comparing existing operations is not likely to substantially advance our treatment of POP. Thus, an improved understanding of the mechanisms responsible for POP (and how they relate to operative failure) is needed. Although several major knowledge gaps were identified at the conference, we focus on four important and broadly defined issues that require urgent attention in future studies.

In the last 30 years, scientists have built upon the discoveries of prior generations, which had focused on remarkably detailed anatomic characterization of the female pelvis. In recent decades, scientists have applied new tools including neurophysiology, imaging (ultrasound

and MRI), cell biology, and molecular genetics to study the biology of pelvic connective tissue and muscle. Despite these efforts, we still do not understand the basic mechanisms that lead to the development of POP.

Individual groups of investigators have been using biomechanical principles to compare women with and without POP. However, progress is hindered by the lack of a generally accepted conceptual disease model. In complex biological processes where different structures, tissues and processes, are involved, it is not possible to conduct one "experimentum crucis" to determine "the cause" of POP. Rather, the results of many experiments must be reviewed and reconciled to develop a comprehensive disease model. For POP, there is a need to describe interdependence of load bearing structures such as levator ani muscles, connective tissue, and nerves as these structures relate to the bony anatomy and to the proposed components of pelvic support. Furthermore, there is a need to understand how expulsive forces are applied and distributed. This gap in our fundamental understanding of the condition will not be overcome without interdisciplinary teamwork, the introduction of new scientific perspectives, and the assimilation of evidence from a variety of fields. A meeting of multidisciplinary researchers with the goal of creating a draft disease model would facilitate overcoming this barrier. Longer-term strategies to facilitate mechanistic research might include convening a group to periodically review emerging data on POP pathophysiology and to iteratively revise the conceptual disease model, similar to systematic review groups, followed by periodic state of the science meetings.

A second issue that hinders progress is a shortage of investigators (fellows/postdocs, etc.) who are fully trained in relevant research tools that are needed to study a complex condition like POP. Though there has been some gradual improvement, developing mechanisms for attracting, supporting and educating new investigators who can design, acquire funding for, and conduct needed experiments is of utmost importance.

Third, research into pelvic floor disorders requires an accurate understanding of *in vivo* pelvic floor anatomy. At present, opportunities or tools to gain a comprehensive understanding of the correct three-dimensional living human anatomy are limited. Because of this, inaccurate anatomical principles are often used in research and carried forward. Creating opportunities for researchers to gain correct structural information could greatly enhance progress. Long-term solutions could include establishing which teaching tools optimize learning (e.g. cadaver, 3D anatomy programs, serial section review).

Finally, there is a great need to integrate the growing body of basic science knowledge with clinical findings, as new mechanistic insights might lead to clinical trials and novel strategies for treatment of POP. Moreover, insights into why a treatment succeeds in one woman and fails in another could be gained by combining clinical and mechanistic research. Long-term strategies to facilitate such interactions might advance both types of research and improve patient outcomes.

II. Novel Prostheses or Implants that Address Pathophysiology and Provide Mechanical Support

Aside from pessaries, surgical repair constitutes the main therapeutic approach for POP. Consequent to high failure rates and frequent reoperations associated with native tissue repairs, pelvic surgeons have turned to mesh and graft-augmented procedures in many instances. To date, the most commonly used material for the treatment of POP is synthetic polypropylene mesh. This material was established as a standard for sacrocolpopexy and midurethral sling procedures. Then, despite a paucity of data regarding their safety and efficacy, transvaginal mesh-augmented procedures became rapidly and widely adopted after 2005. This was mainly driven by the need to improve clinical outcomes associated with native tissue surgeries, and a desire to provide less invasive surgical options than mesh sacrocolpopexy via laparotomy. The resultant high complication rates associated with transvaginal mesh placement subsequently prompted the US Food and Drug Administration to issue public health notifications in 2008 and 2011 [3]and to upgrade these implants from Class II to Class III medical devices[4]. Despite the uncertainty regarding long-term outcomes of transvaginal mesh procedures, ongoing questions about the complications of this approach, and public perceptions of adverse outcomes, transvaginal mesh for POP remains part of the surgical armamentarium of up to 61% of AUGS members[5]. Thus, there is a pressing need to develop safe, durable and minimally invasive surgical treatment alternatives for women with POP. Novel graft and/or mesh materials that provide mechanical support, while maintaining compatibility with native vaginal tissue have a high potential to address the above unmet need.

A major barrier hindering progress is our incomplete understanding of the host tissue mechanical properties that surgeons are trying to replace with mesh and/or grafts. The physiological loading conditions imposed on the pelvic support structures and variability across different phases of life (e.g. adolescence, pregnancy, after menopause) are still poorly understood. Thus, the alterations in loading on the pelvic floor that lead to POP remain largely unknown, and cannot be extrapolated from orthopedic or general surgery literature. Consequently, when mesh or grafts are developed to provide vaginal support, we are unable to identify the best locations for attachment and to determine how well various anchoring points replicate the physiological load distribution on the pelvic supportive structures. Therefore, an important initial step is to clarify the main mechanical goals of graft-augmented pelvic surgeries. This would allow for more effective collaborations with engineers and basic scientists from other disciplines.

An incomplete understanding of the key features of *in vivo* host responses to mesh and/or graft materials and how these correlate with clinical outcomes blocks progress. As we move forward with the development of novel materials, we must simultaneously create tools that enable identification of the subset of patients that have an innate ability to regenerate a high quality supportive connective tissue or muscle. We need clarity on patient-level factors that provide an optimal environment for functional mesh or graft “integration” and which factors differentiate patients who develop mesh or graft-related complications. Additionally, we must understand how the host response to mesh or graft materials evolves over time, and how it differs from the default response to surgery and implantation of a foreign body. To

achieve the above, an infrastructure for the collection of pre- and post-operative biospecimens from patients undergoing native tissue and mesh and/or graft-augmented POP repairs should be built, along with the appropriate quality control measures and staff to maintain specimens.

III. Large-Scale Community-Based Research

Over the past 20 years, epidemiologic research has revealed that POP is highly prevalent: more than 1/3 of adult women demonstrate stage 2–4 pelvic organ support and 13% undergo surgery for POP by age 80[6, 7]. Longitudinal studies suggest that mild POP does not inevitably progress and may actually regress over time[8, 9]. Epidemiologic research has also uncovered some important risk factors for the development of POP, such as age, obesity, and familial predisposition,[10] and has demonstrated the critical influence of vaginal childbirth[11]. However, important questions remain unanswered.

Prevention research is currently limited by our imperfect understanding of who is at greatest risk of developing POP. Further large-scale research is needed to identify genetic and phenotypic risk factors, as well as to understand the contribution of lifestyle, nutrition, obstetrical experiences, comorbid medical conditions, and other environmental influences. Longitudinal studies are required to investigate how various biological and environmental factors affect the course and progression of pelvic organ prolapse across a woman's lifespan. After discussion, three priority areas were identified that would facilitate large-scale community-based research.

The first is the development of robust and inexpensive research tools for use in large-scale studies. This requires a standard set of "best outcome measures" that are reproducible and able to be incorporated into large-scale studies. Furthermore, there is value in developing patient self-assessment tools and/or simple assessments that could be incorporated into primary care settings. Modifications of current diagnosis and procedural codes to better distinguish clinically-meaningful POP subtypes would facilitate more relevant administrative and health services research. Finally, the field would be advanced by the creation of instruments for assessment of lifestyle and behavioral factors that impact POP.

A second priority is to promote research to better understand biologic risk factors for POP development, progression or recurrence. This includes scientific partnerships to investigate biological factors and their association with clinical phenotypes. Specimen repositories that link with clinical and research databases would be helpful.

Finally, a particularly important priority is the development of prevention strategies for POP. This requires the development of a rigorously tested conceptual framework to address prevention across a woman's lifespan. Researchers should promote the development of mathematical prediction models to identify women at greatest risk for POP and for POP recurrence. These prediction models should include research on modifiable risk factors that could minimize POP progression or recurrence and could also include mechanistic measurements (such as muscle strength or other biomarkers).

In summary, epidemiologic research in POP plays a vital role in improving our understanding of POP and may facilitate POP prevention and treatment. This scale of research will require the creation of partnerships across societies, industry, government, academic institutions, and the private sector (community practice).

IV. Clinical Trials to Optimize Outcomes After POP Surgery

Well-designed randomized clinical trials provide the highest level of evidence on treatment safety and efficacy, and surgical trials have played a critical role in advancing our understanding of the treatment of POP. Certainly, rigorous multicenter trials have provided important knowledge about long-term outcomes after mesh sacrocolpopexy and comparative outcomes after different types of vaginal vault suspension[2, 12]. However, despite significant advances in the last 20 years, three fundamental research issues remain unanswered: 1) what are the most effective surgical approaches for prolapse that also minimize complications; 2) which situations call for biologic graft or synthetic mesh augmentation versus native tissue repair; and 3) whether or not to remove the uterus (if present) at the time of POP surgery. Importantly, these issues may be influenced by patient characteristics such as age, comorbidities, sexual function, physical activity, and tissue quality. Moreover, a variety of physician factors may also influence the route and choice of surgical approach, such as physician training, experience and bias/preference.

Generally, successful POP trials have had simple and clear inclusion and exclusion criteria that balance specificity and generalizability. Use of valid, reliable, outcome measures in multiple domains (i.e. objective anatomic outcomes as well as patient-reported and quality of life outcomes) is necessary to capture the full impact of POP treatments. Masking patient assessments, in particular physical examinations, is important to minimize bias. Challenges that remain include physician bias, patient reluctance to accept randomization, the inefficiency of clinical trials to evaluate new technologies in a rapidly changing field, and the medico-legal environment. Additionally, few POP trials follow patients for more than 1–2 years. Given the high risk of recurrence, there is a critical need for long-term follow-up studies (5–10 years or more). There is also a need for large pragmatic trials to provide patient-centered effectiveness information. Finally, there is a need to understand the risks and benefits of POP treatments for specific patient subgroups so treatments can be tailored and individualized to optimize outcomes. Promoting the development of standardized measurable outcomes, research to identify predictive biologic and/or clinical phenotypes, and innovative approaches while balancing safety will be important steps to facilitate POP surgical and clinical trials of the future.

V. Development of evidence-based quality measures for prolapse outcomes

In an era of quality-focused health care, it will be important to develop meaningful measures of quality for the care of women with POP. Several types of quality measures (e.g. outcome measures, process measures, patient centered outcomes, and cost/resource use) can be used to assess care. The scientific acceptability of a proposed measure depends on supporting data, guidelines for implementation of the measure, data confirming the validity and reliability of the measure, and evidence suggesting that there are opportunities for practice improvement in the relevant area.

Currently, three *outcome measures* exist that apply specifically for POP procedures, and all pertain to the reporting of complications after POP repair surgery - specifically bladder, ureteral and bowel injury (PQRS #432,433,434). Creation of a more robust collection of quality measures that focus on long-term outcomes is limited by the lack of globally accepted outcome measurement criteria. The pelvic organ quantification system (POP-Q) examination, an objective assessment of POP anatomy, has not been universally adopted, and anatomic definitions of success or failure are not universal. For subjective evaluation of outcomes, there are many validated questionnaires used to assess POP, but there is no consensus about their use or about scoring that could be used to define failure or success. Thus, an accepted set of "best outcome measures" would be very helpful towards the development of rigorous quality outcome measures for the treatment of POP. Furthermore, scientifically rigorous data about surgical outcomes would provide the ability to benchmark surgeon performance. Patient reported outcomes for POP have not been well studied or defined, and there are currently no validated patient-reported outcome tools for use in patients with POP. These barriers are likely to be overcome by collaborating with clinical trialists and epidemiologists to create the data that can be incorporated into quality measures in the future.

In addition to *outcome measures*, there are nine *process measures* in use or development for reporting to the Centers for Medicare and Medicaid Services: 1) cystoscopy at the time of hysterectomy (NQF#2063, PQRS #422); 2) apical suspension (i.e. suspension of the most proximal or superior portion of the vagina) at the time of hysterectomy for POP; 3) assessment of POP prior to surgical repair (Merit Based Incentive Payment System); 4) offering a pessary (Merit Based Incentive Payment System); 5) use of a pessary (Merit Based Incentive Payment System); 6) preoperative assessment of SUI prior to POP surgery (NQF# 2677, PQRS# 428); 7) assessment of sexual function prior to POP repair (Merit Based Incentive Payment System); 8) exclusion of uterine malignancy prior to obliterative procedures (i.e. procedures that close the vaginal cavity and may in theory prevent access to internal organs for diagnosis or treatment) (PQRS#429); and 9) rectal examination during posterior compartment POP repair (MIPS). Similar to outcome measures, process measures are also hampered by limited agreement regarding outcomes, as creation of these measures depend on actionable direction from systematic reviews and guidelines. Clear and actionable items are infrequently offered because of the challenges involved in linking processes to weakly defined outcomes. In addition, data regarding risk stratification and disparities in care within Female Pelvic Medicine and Reconstructive Surgery are lacking.

There are critical initiatives that would facilitate the creation of new evidence-based quality measures for POP treatment. The development of a generally accepted measure of success (or failure) of surgery for pelvic organ prolapse could facilitate the successful measurement of surgical outcomes as well as the creation of process measures that can be tied to outcomes. This effort is best led by a national professional organization that can promote the use of such a measure for research and clinical care purposes. Characterization of patient expectations and satisfaction regarding preoperative evaluation, the perioperative experience, and postoperative recovery expectations and limitations are a critical element to developing successful patient-centered outcome (PCO) tools. Examples of such tools used to assess surgical outcomes in other fields include the "breast-q"[13] that evaluates PCO's for patients

undergoing breast reconstructive surgery. Similar tools may be useful in women undergoing POP surgery. Finally, research using large data sets to describe the events and healthcare costs associated with typical patterns of care for a patient with POP can be used to develop measures of efficiency and cost-effective care.

Discussion:

The AUGS 2016 Prolapse Consensus Conference brought together researchers, clinicians, industry representatives and patient advocates to review the current state of POP research and identify priority areas for future research where progress is most likely to impact clinical care and patient outcomes. We anticipate that the results summarized in this report will promote increased collaboration among researchers with diverse expertise, will serve to support the importance of POP research overall, potentially focus efforts in key areas which may rapidly improve care of POP patients, and may spur an interest for POP research among students and trainees in our urogynecology community.

The Conference presentations and discussions centered around 5 critical topics, which arose from surveys of health care professionals and AUGS members. The priority areas identified for future research and summarized in this report include a wide spectrum of research types and disciplines, but common threads that would advance POP research were noted across the 5 topic areas. One such common thread is the pressing need for a standardized group of outcomes for POP, or the set of “best outcome measures” that could be utilized in large trials, community based research, and quality measures. We also saw many groups focus on the need for personalization of treatments and identification of factors that would allow for more successful individualized care. The ability to personalize treatments often depends on a combination of rigorous bioinformatics, biological data, and knowledge of outcomes over a clinically relevant period of time. Thus, several workgroups identified the need for specimen biorepositories that can integrate with clinical data, and the capacity for this type of information to substantially advance research in POP. Finally, the ability to integrate different types of data for a complex condition like POP requires collaborative, multidisciplinary research groups. These groups currently exist in specific institutions, but attracting more trainees with higher quality research training may expand this type of collaborative research to allow our scientific community to tackle more challenging and complex questions.

One unique aspect and strength of the 2016 Prolapse Consensus Conference was that multiple stakeholders with diverse perspectives were included as presenters and attendees. An effort was also made to include patient advocates, trainees and junior researchers in the workgroup discussions; these stakeholders contributed valuable insights across all topic areas. The Consensus Conference attendees were surveyed about the conference, and the overall response showed enthusiastic support for the format. Suggestions for improvements were also collected and generally focused on the need for enhanced advance communication to ensure adequate and broad participation from multiple perspectives.

In summary, the 2016 Prolapse Consensus Conference provided a venue to identify areas of POP research priority, and an opportunity to collaboratively brainstorm about ways to

improve the science of POP research. Suggestions from this conference will be considered carefully by the AUGS Scientific Committee and Board of Directors as they consider how AUGS might support POP researchers and existing research efforts in these critical areas.

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