GI Issues

Introduction

Dr. Colleen Hadigan, MD, MPH, presented on "The Quest for Continence: A Review of Gastrointestinal Issues in PMS". Her presentation focused on reviewing existing literature regarding gastrointestinal (GI) issues in individuals with PMS as well as providing newer research data from a recent natural history study and PMS registry.

Prior literature indicates that GI and related issues are highly prevalent among individuals with PMS. For example, approximately 40% of individuals have reported issues with constipation or diarrhea, approximately 85% of individuals demonstrate pica, and 42% of individuals have gastroesophageal reflux disease (GERD). In addition, only approximately 24% of individuals with PMS are toilet-trained. Dr. Hadigan also suggested that the high rate of hypotonia in the PMS population (75%) might contribute to GI and related issues.

In a recent natural history study examining 14 patients with PMS, numerous GI and food related symptoms were reported. Constipation and choking/gaggling each were reported in approximately 36% of the sample. In addition, GERD, difficulty swallowing, abdominal pain, food intolerance, diarrhea, and vomiting were reported. Food allergies were relatively uncommon among the patients; however, approximately 35% of patients were on gluten- and casein-free diets. Regarding treatment for GI symptoms, 79% of patients were reported to have a lifetime history of GI medication use and 57% of patients were reported to currently be using mediation. No patients in the study were reported to be using an enteral tube for feeding. Body-mass composition index (BMI) varied widely among patients, with approximately 29% of patients having a BMI over the 80th percentile range (i.e., overweight) and another 29% of patients having a BMI under the 10th percentile range (i.e., underweight). Lastly, in a GI study currently being conducted at the NIH (Sitz Marker study), which examines colonic motility in patients with PMS, revealed that two patients had abnormal retention (e.g., rectal outlet dysfunction), but neither patient showed evidence of dysmotility.

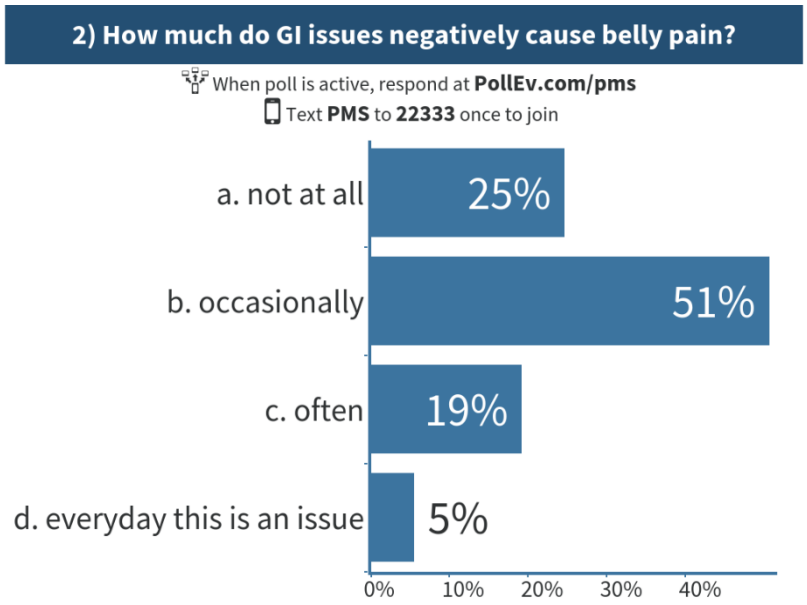
Additional data was presented regarding toilet training of individuals with PMS. Parent-reports from the PMS Registry indicated that approximately 73% of individuals with PMS are not yet able to toilet independently, with an estimated 15% of individuals occasionally and 13% of individuals always being independent with toileting. Data from the NIH GI Evaluation also indicated that an estimated 55% of parents expressed that toilet training continues to be a goal. The NIH GI Evaluation also documented that 71% of parents reported primary incontinence as being a present issue.

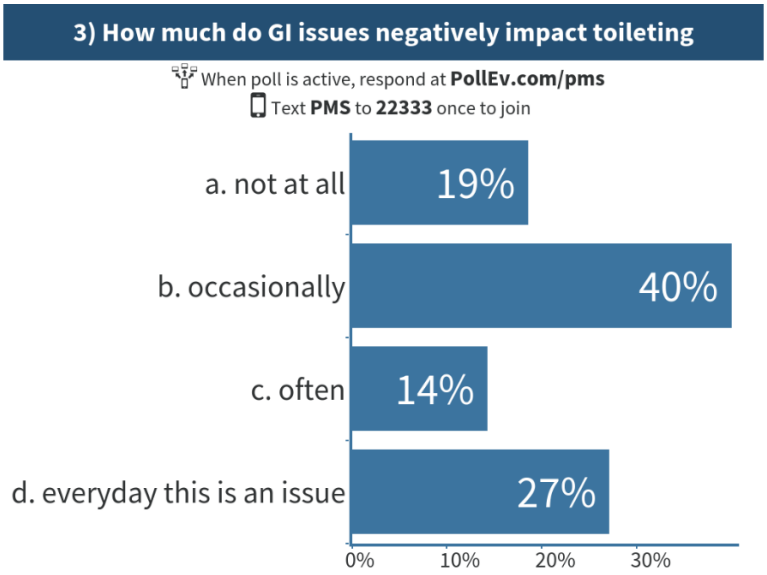
There is some support for a relationship between GI issues and intellectual functioning in individuals with PMS. For example, Dr. Hadigan reported a relationship between verbal IQ and GI issues, with individuals with lower verbal IQs having increased GI issues. Related data presented suggested that smaller deletion size has been associated with higher probability of toilet training success.

Identified Problems

1. **My child's GI issues are a serious concern for me and negatively impact my child's life.**

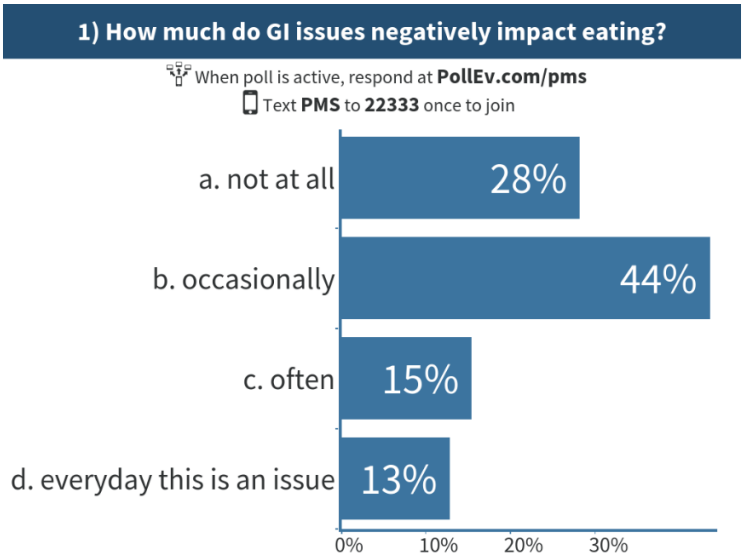
Consistent with prior literature, the Group discussion indicated that individuals with PMS demonstrate numerous GI issues. The primary GI concerns reported by parents included constipation and specific feeding issues (i.e., oral-motor difficulties, gagging and swallowing issues, and rumination). At least fifty-three parents indicated that constipation was an issue for their child and endorsed it being a moderate concern (3.9 out of 5). Specific issues related to constipation that parents noted included, but were not limited to: dietary changes and changes in routines worsening constipation, pain and discomfort associated with constipation, impact on child's behavior and mood, and overall impact on family life/daily routine. For example, several parents described behavioral changes in their children during bouts of constipation, specifically noting the children being "antsy" and demonstrating "lack of attention." According to the Poll Everywhere poll, approximately 51% of parents reported occasional belly pain in their children (see Question 2 graph below). Another parent also described "scheduling her day" around her daughter's constipation issues, especially as it related to toileting. The Poll Everywhere data was consistent with this complaint. Approximately 27% noted the daily impact of GI issues on toileting and an additional 40% noted the occasional impact of GI issues on toileting (see Question 3 graph below).





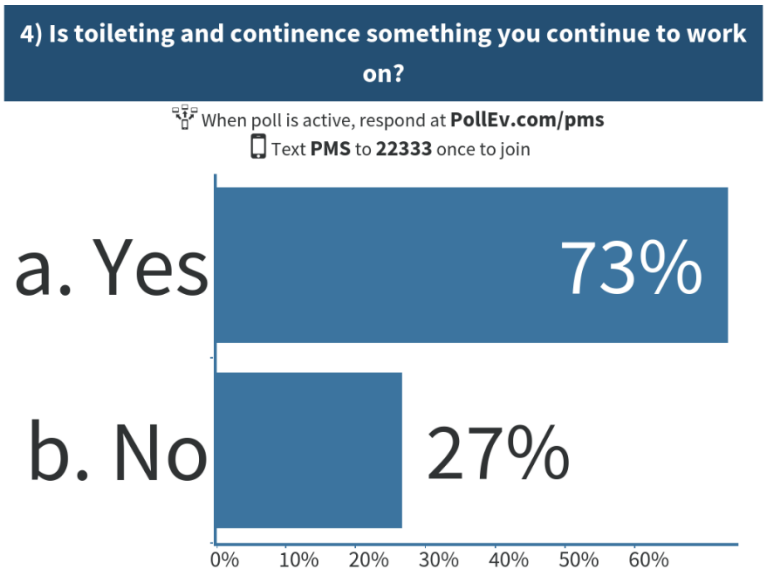
Furthermore, during the Group discussion, at least forty-three parents indicated that additional feeding issues, including swallowing difficulty, gagging/choking, reflux, and rumination, were a problem from their children and endorsed it to be a severe concern (4.7 out of 5). These documented problems may be related to the 44% of parents who indicated that GI issue negatively impact eating occasionally and an additional 28% who indicated that these issues impact eating often or daily based upon results from Poll Everywhere (see Question 1 graph below). Parents also endorsed specific concerns regarding feeding issues. For example, parents noted that because their children cannot keep food down their children were not gaining weight or growing properly. Chewing and swallowing difficulties also were noted to limit the variety of food in the children's diets and required "excessive" and "expensive" food preparation. Cyclical vomiting also

was a recurring concern noted by parents. Overall, GI issues (including feeding issues) were noted to have a negative impact of the children's and families' quality of life.



2. Toilet training has been a serious challenge for my child.

Difficulties associated with toilet training and continence were rated as a moderate to severe concern for parents (4.1 out of 5), and at least 47 parents reported this being a primary issue during the Group discussion. Additionally, Poll Everywhere data indicated that approximately 73% of parents reported that toileting continues to be an active goal for their children with PMS (see Question 4 graph below). However, it is unclear whether the remaining 27% of parents constitute parents who no longer need this as a goal because continence has been achieved or because parents have chosen to no longer pursue toilet training as a goal. Parents who endorsed difficulties related to toilet training questioned whether specific methods of toilet training were more successful for individuals with PMS. For example, one parent sought out "general guidance around when to start toilet training with a nonverbal child." The parent went on to ask, "What [kind of] motivation to promote not having wet/dirty diaper? Do[es] [the child] need to be able to sit? Are we missing an important window? Is there a link between motor skills and being ready to toilet?" Although this was one parent's experience prior to the toilet training process, similar questions and concerns were brought up for parents who both had not yet started or who had started the toilet training process but had not had success. These questions suggest two themes related to toilet training parents are seeking knowledge about. First, the most effective methods of toilet training to teach a child with PMS (e.g., "Should I put my child in Pull-Ups?) Second, identification of specific challenges associated with toileting that may be related to the PMS diagnosis/primary or secondary symptoms (e.g., Is there hope for potty training later in the age group [when motor and developmental skills higher]?".



3. The underlying nature of my child's GI issues are poorly understood and few studies are assessing this research question.

During the Group discussion, at least 35 parents reported having questions regarding the nature of their children's GI issues and what research studies were being conducted to answer this question. This was rated as a moderate-to-severe concern for these parents (4.2 out of 5). Specific questions asked by parents include "Are the neurons in the bowel system related to SHANK3?" "Are [my child's GI issues] related to physical or behavioral/psychological issues?" and "Would bacterial analysis of feces be able to predict which PMS kids have/will have GI issues?" Additionally, parents reported concerns regarding the limited number of research studies examining GI issues in individuals with PMS and that those research studies that did had limited inclusion criteria. For example, one parent whose child has chronic intestinal pseudo-obstruction with colonic intestinal failure and receives continuous Total Parenteral Nutrition (TPN) indicated that the child was excluded from NIH GI study because of TPN use. Similarly, the Panel discussion included several questions regarding the etiology of GI issues.

4. I am not sure how to help my child's GI issues.

Parents who indicated that their children had GI issues also reported concerns related to appropriate treatment and intervention for these GI issues. As the majority of parents indicated constipation as being a primary concern, treatment for constipation also was the focus of the Group discussion. At least 44 parents endorsed concerns related to treatment of GI issues, and the concerns were rated to be of moderate significance (3.3 out of 5). Over-the-counter medications (e.g., Miralax) were identified by parents as helping to relieving constipation; however, parents also questioned whether additional over-the-counter or prescription medications also would be useful (e.g., enemas, zinc).

Further, parents questioned the use of probiotics and dietary changes to help alleviate constipation and assist in achievement of toilet training during both Group and Panel discussions. For example, one parent asked "Can probiotics or something else help assist it getting full bowel movement and bladder control?" and another asked "[Are dietary changes] good for behavioral as well as physical reasons for GI issues?"

Proposed Solutions

1. **Development of GI practice parameters to assist families struggling with GI issues and the medical providers treating them.**

Specific practice parameters related to GI and feeding issues should be developed to: 1) help families identify common GI issues in individuals with PMS; 2) help families determine appropriate treatment course for each of these common GI issues (i.e., work with general practitioner, seek consultation from specialist); 3) assist general and specialized medical providers in treating GI issues within PMS population (i.e., specific concerns within this population, additional tests needed to be ordered); and 4) identify "gold-standard" protocols for treating the common GI issues. These practice parameters, which should be based on existing literature as well as PMS Registry data and data being collected through clinical research studies, can be used a road map for families (and the medical care providers) to best serve the needs of the individual with PMS regardless of GI issue. Given the negative impact GI issues have on individuals with PMS and their families, the development of this document may help reduce some of the stress associated with these issues. Thus, it also is important for these practice parameters to be mindful of the unique challenges associated with GI issues in the PMS population. For instance, a tool-kit or parent-guide also should be developed alongside these practice parameters to help parents deal with these daily challenges at home. This tool-kit may contain food/toileting diaries, social stories about going to the GI specialist, and support for parents.

Within the practice parameters (primarily for medical providers) as well as parent tool-kit, treatment options should be detailed for specific GI issues. Additionally, providers and parents should be aware of alternative treatment practices that have not been supported by research and may be harmful to individuals with PMS. For example, Dr. Hadigan indicated that the use of probiotics is "not recommended" due to the lack of evidence supporting its use in this population. Information like this is not readily available to parents, and thus it is important for increased dissemination of research findings in lay-friendly avenues to be made readily accessible and available.

2. **Development of toilet training guide book to help aid in toilet training process.**

As toilet training has been identified as a major challenge for most parents of individuals with PMS, a tool-kit dedicated specifically to toilet training practices should be developed. Similar tool-kits exist for parents of individuals with ASD, and thus it may be appropriate to adapt this tool-kit for parents of individuals with PMS. This tool-kit also should be mindful to include specific challenges related to toilet training individuals with PMS (e.g., motor and speech delays/impairments).

3. Increased research into the types of GI issues affecting individuals with PMS and potential underlying biological and psychological pathways.

Due to the prevalence of GI issues affecting individuals with PMS and its impact on quality of life, increased research should be dedicated into the underlying mechanisms of GI issues in PMS. By better understanding the nature of these issues, it can better inform research studies examining effective treatments for GI issues in individuals with PMS. Research studies should aim at examining the common GI issues (e.g., constipation, diarrhea, swallowing issues, reflux) at multiple levels (i.e., psychological, structural, molecular). Information regarding participation research studies should be readily accessible to families via research lab and PMSF websites. Additionally, the dissemination of research results also should be more accessible to families (e.g., PMSF website, vlog).