Working title:

Menstruation and Menopause in autistic adults: Periods of importance?

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Abstract

Autism spectrum conditions (ASC) were once seen as a predominantly male. This has caused a paucity of information on common events in the lives of women, such as menstruation and menopause. Some smaller studies indicate that autistic individuals might suffer from increased difficulties surrounding these events. This study aims to investigate, whether autistic individuals experience more frequent premenstrual dysphoric disorder (PMDD), and increased complaints surrounding menopause.

In 70 individuals (ASC n=28, comparisons n= 42) we did not find an increased prevalence of PMDD in autistic individuals (14.3%) compared to non-autistic individuals (9.5%) . Autistic individuals 40 (n=75, ASC n=30, comparisons n= 35) did experience higher levels of menopausal complaints. In autistic individuals, higher menopausal complaints were associated with higher levels of depression and autistic traits. In non-autistic individuals, menopausal complaints were associated with increased inattention, hyperactivity/impulsivity (i.e., ADHD traits), and depression.

With this work, we show the important role that major reproductive milestones can have in an autistic woman's life.

Lay abstract

Autism spectrum conditions (ASC) were once seen as a predominantly male, but this has caused research to have little focus on women. Therefore, little is known about menstruation and menopause in ASC. Some smaller studies indicate that autistic individuals might suffer from increased difficulties surrounding these events.

This study aims to investigate, whether autistic individuals experience more frequent premenstrual dysphoric disorder (PMDD), causing extreme physical, emotional and functional impairment. We also examined whether individuals with ASC experience increased complaints surrounding menopause.

We did not find an increased prevalence of PMDD in ASC (14.3%) compared to non-autistic individuals (9.5%) . Those with ASC did experience increased menopausal complaints. These menopausal complaints were associated with higher levels of depression and autistic traits. In non-autistic individuals, menopausal complaints were associated with increased inattention, hyperactivity/impulsivity (i.e., ADHD traits), and depression.

With this work, we show the important role that major reproductive milestones can have in an autistic woman's life.

As Autism Spectrum Conditions (ASC) have once been seen as a predominantly male condition, far fewer studies have focused on ASC in women¹ (Loomes, Hull, and Mandy 2017). Moreover, as the classification itself is only now reaching adulthood, there is a shortage of information about autism in adulthood in general (Lai and Baron-Cohen 2015). Although we know that major reproductive milestones (e.g., menstruation, menopause) can have major effects on the lives of women (Schneider and Birkhäuser 2017; Schoep et al. 2019), currently few studies focus on how these affect autistic women², even though there is some indication that autistic women are differently affected by these hormonal changes (Moseley, Druce, and Turner-Cobb 2020b, 2020a). As this could indicate a differential need in autistic and non-autistic women, it is of the greatest importance to address this knowledge gap, by mending this imbalance in research.

During the late luteal phase, in the week before menstruation, around five to eight percent of women (Cohen et al. 2002; Wittchen et al. 2002) experience debilitating emotional and physical symptoms, combined with functional impairment, also called premenstrual dysphoric disorder (PMDD) (American Psychiatric Association 2013). PMDD is often comorbid with mood and anxiety disorders (Wittchen et al. 2002), but also appears to be associated with comorbidities that one might expect less such as substance use disorder (Fernández et al. 2018; Kepple et al. 2016) or schizophrenia (Ullah et al. 2020). Also in ASC, there is evidence of a higher prevalence of PMDD. Lever and Geurts (2016) reported that almost 21% of autistic women- compared to 3% of non-autistic women- suffered from PMDD. An much more worrying percentage is reported by Obaydi and Puri (2008), where it was found that 92% of autistic women with learning disabilities experienced late luteal phase dysphoric disorder (an earlier description of PMDD) compared to 11% of non-autistic women with learning disabilities. Although evidence is currently limited to two studies with relatively small sample sizes, both studies point to a higher prevalence of PMDD in autistic women.

¹ In the current manuscript we include every individual who menstruates, regardless of gender. as all individuals included in this manuscript identified as cisgender, we will continue to use “women”. Sex is the label you are assigned at birth, related to a persons’ biology, anatomy and chromosomes, while gender is based on social and cultural expectations, norms, views and behaviors associated with a specific sex. Importantly, sex and gender are often used interchangeable, however even though both can influence research results, they represent a different concept.

² We use identify first language (also see Kenny et al., 2016) throughout this manuscript. However, we want to note the lively discussion about person first, vs identity first language.

If increased PMDD in autism is associated with increased hormonal fluctuations (as argued by Obaydi & Puri, 2008), one can expect that also more severe complaints are experienced during menopause. The menopausal transition is characterized by large fluctuations in hormones (perimenopause), until after 12 months without menstruation post-menopause sets in. In this transitional phase women experience many physiological changes which cause a wide variety of physical, psychological, sexual, and social problems (Nelson 2008). Two qualitative studies investigating autistic women's experience of the menopausal transition indicate that there are reasons to believe that this is a particularly difficult life phase, associated with large unmet (health) needs (Moseley et al. 2020b, 2020a). Unfortunately, due to the qualitative nature of these studies, and the lack of a comparison group, no inferences can be made whether this is specific for autistic women.

Next to diverging and/or more severe symptoms typically associated with hormonal changes, there are reports that autistic characteristics (such sensory differences and difficulties with regulating behaviors) are increased during menstruation (Steward et al. 2018), and menopause (Moseley et al. 2020a, 2020b). This heightening of autistic characteristics during menopause might be the reason that autistic women are more often diagnosed during menopause (Moseley et al. 2020b). Moreover, in non-autistic women, menopausal symptoms are often associated with higher rates of psychiatric/psychological symptoms (Nelson 2008). It is unclear how the menopausal transition affects psychiatric/psychological symptoms in those already at a higher risk of psychiatric/psychological symptoms (i.e., women with ASC). Therefore, we will explore the relation between menopausal symptoms and psychological symptoms in which we will focus on the top three associated mental problems in ASC (anxiety, depression, and ADHD, see (Lever and Geurts 2016)).

This preregistered study (AsPredicted #49299) aims to i) replicate findings by Lever & Geurts 2016 and Obaydi & Puri 2008 showing a higher prevalence of PMDD in autistic women; ii) explore whether autistic women also experience more/different menopausal symptoms during the menopausal transition iii) explore the relation between menopausal symptoms and symptoms of ASC, anxiety, depression, and ADHD.

Method

Participants

Participants were recruited via several clinical institutions across the Netherlands, (social) media advertisements of autism networks, and the social network of the researchers, research assistants, and students. The current study uses data of those participants that were newly recruited during Wave 3 of an ongoing study for analyses concerning PMDD, also see (Geurts et al. 2021). The following exclusion criteria were applied to all participants in the current study: (a) intellectual disability and/or IQ-score <70, (b) insufficient understanding of Dutch language, (c) a history of neurological disorders (e.g., epilepsy, stroke, multiple sclerosis), schizophrenia or having experienced more than one psychosis) current alcohol or drugs dependency. For the comparison group were supplemented with (a) one or more psychotic episodes, (b) present/past diagnosis of an ASC or a total score higher than 32 on the AQ or ASC in close family members (i.e., parent(s), child(ren), brother(s), sister(s)) (c) present/past diagnosis of ADHD or a total score of six or higher on the ADHD-SR or a diagnosis of ADHD in close family members. Participants in the ASC group were required to have a clinical DSM (IV or 5)-diagnosis of an ASC. For analyses concerning PMDD, we used all newly recruited participants (i.e., not included in Lever & Geurts (2016)) that were interviewed (n=70, ASC n=28, comparisons n= 42). For analyses concerning menopausal complaints, we used all participants older than 40 (n=75, ASC n=30, comparisons n= 35) with self-reported irregular or absent menstruation patterns. Samples were partly overlapping.

Materials

PMDD [yes/no] was taken from the Mini international neuropsychiatric interview Plus (MINI-Plus; Sheehan et al. 1997; Van Vliet, Leroy, and Van Megen 2000). This is a structured diagnostic interview that explores several psychiatric disorders. We used lifetime prevalence, and this was assessed retrospectively in peri/postmenopausal women.

Menopausal complaints were examined using the Dutch version of the Menopause Rating Scale (MRS) (Heinemann, Potthoff, and Schneider 2003; Schneider et al. 2000). Total score, and three subscale scores i.e., psychological symptoms such as depression and anxiety (0-16); somato-vegetative symptoms including hot flashes and cardiac complaints (0-16) and urogenital symptoms such as sexual complaints and vaginal dryness (0-12) were used.

Psychiatric/psychological symptoms were measured by subscale scores of the SCL-90 (Arrindell and Ettema 2005; Derogatis 1977) for depression, and the sum of anxiety and agoraphobic anxiety as a proxy of anxiety.

Furthermore, we used the ADHD-SR (Kooij et al. 2005) to assess current ADHD symptoms, subdivided in inattention and hyperactive/impulsive symptoms.

Total score on the Autism Quotient (AQ) was used to assess autistic characteristics (Baron-Cohen et al. 2001; Hoekstra et al. 2008).

Procedure

Written informed consent was obtained from all participants. The study was approved by the ethical review board of the Department of Psychology of the University of Amsterdam (2018-BC-9285). The current study was performed conform the principles of the Declaration of Helsinki Declaration of 1975, as revised in 2008. Participants underwent extensive testing protocol (for a full description of all procedures see Geurts et al., 2021). Data used in the current study were obtained during Wave 3 of a longitudinal overlapping cohort study and concerning PMDD only data was used of participants that were newly recruited during Wave 3. Participants received compensation for travel and a small reward for participation.

Community involvement

A stakeholder group consisting of autistic individuals is involved in all major aspects of the current research. The group meets 3 or 4 times a year, and during this meeting topics like study design, materials, results, and dissemination of results are discussed. The stakeholders receive compensation for their participation.

Data analyses

All frequentist analyses are performed in R (RStudio Team 2015). Age, IQ, MMSE, and AQ differences among groups were examined using a *t*-test. For education, a chi-square test will be used. To test our first hypothesis, whether autistic women experience lifetime PMDD more often than non-autistic women, a χ^2 test were used. Next, our second hypothesis, whether the number of menopausal complaints differ between groups, were tested using a *t*-test with group (ASC/COMP) as the independent variable and MRS total score and subscales as the outcome.

Bayesian analyses with default priors were performed in JASP (JASP Team 2020) to assess group effects. BF_{10} expresses the probability of the data given H_1 relative to H_0 , BF_{01} expresses the probability of the data given H_0 relative to H_1 (please note that $BF_{01} = 1/BF_{10}$). Bayes factors larger than 3 can be interpreted as substantial or stronger evidence for H_1 (Lee and Wagenmakers 2014).

To assess whether MRS scores are associated with psychological/psychiatric symptoms (depression, anxiety and ADHD symptoms), regression analyses will be performed. Separate models for the separate subscales of the MRS will be run. Moreover, we will explore whether relations differ between groups by adding the interaction with group to our models. In addition to our preregistration, we will assess whether autistic characteristics are associated with menopausal complaints. Correction for multiple comparisons will take place using the Benjamini-Hochberg correction for four tests for all analyses with MRS as outcome.

Results

Participant characteristics

For our analyses for PMDD, information was available for 28 autistic women and 42 non-autistic women. The autistic women had more autistic symptoms, but groups did not differ in IQ, age, education, or MMSE score (also see Table 1, upper panel).

For analyses concerning menopausal complaints, data was available for 30 autistic women and 35 non-autistic women. Again, autistic women had more autistic symptoms, but groups did not differ in IQ, education, age, or MMSE score (also see Table 1, lower panel).

{insert table 1 here}

PMDD

Lifetime PMDD was reported by 14.3% of autistic women and 9.5% of non-autistic women.

This difference was not statistically significant ($\chi^2(1)=.38$, $p=.54$), and this lack of group differences was supported by Bayesian statistics ($BF_{10}=.33$, Table S1)

Menopausal complaints

Autistic individuals had higher total menopausal complaints than non-autistic individuals (Figure 1). This translated into higher scores on subscales of psychological complaints, and somatic complaints, but not for urogenital symptoms (Table 1 lower panel). These results are supported by Bayesian statistics, except for urogenital symptoms where there was no evidence for either hypotheses (see supplementary Table S1).

{insert figure 1 here}

As autistic individuals also scored higher on measures of anxiety, depression, autistic characteristics, inattention and hyperactivity impulsivity, regression analyses were performed separately for autistic and non-autistic individuals. Total menopausal complaints were related to depressive symptoms in autism, but not in comparisons. In non-autistic women, significant associations were observed between total menopausal complaints and symptoms of inattention and hyperactivity impulsivity. No other significant associations were found between total menopausal complaints and psychological/psychiatric complaints (also see Figure 2).

{insert figure 2 here}

Psychological menopausal complaints were associated with depressive symptoms in both groups, and with autistic characteristics in autistic individuals. One autistic individual had extreme menopausal complaints (total score of 33). The association between total menopausal complaints and depression scores in autism was dependent on this participant and was no longer significant and smaller ($r=.09$) after removal (Supplementary Table S2).

{insert table 2 here}

Discussion

In autism research men have been overrepresented for decades (Loomes et al. 2017), leading to a paucity of knowledge about common events in the lives of autistic women, such as menstruation and menopause. With this study we aimed to investigate the prevalence of PMDD and menopausal complaints in autistic women. In contrast to our hypothesis and previous studies (Lever and Geurts 2016; Obaydi and Puri 2008), we did not find that autistic women suffer from PMDD more often than non-autistic women. However, as hypothesized we found that autistic women do experience more menopausal complaints. Moreover, we explored whether these menopausal complaints were associated with common psychological/psychiatric complaints in both autistic and non-autistic women. Confirming our hypothesis, we found associations between menopausal complaints and psychological/psychiatric complaints in both autistic and non-autistic women.

We did not replicate findings (Lever and Geurts 2016; Obaydi and Puri 2008) of increased lifetime prevalence of PMDD in autistic compared to non-autistic women. In our sample autistic women reported a somewhat higher prevalence of PMDD (i.e., 14.5%) compared to previous studies in community samples of non-autistic women (around 8% (Dennerstein, Leher, and Heinemann 2012; Wittchen et al. 2002; Yonkers and Simoni 2018). Autistic women in the current sample reported a lower prevalence of PMDD compared to previous studies on PMDD (Lever & Geurts, 2016 [21%]; Obaydi & Puri, 2008 [92%]). As reported prevalence rates of PMDD in autistic women vary so immensely between studies (14.5%-92% of autistic women), studies in larger samples with more fine-grained measures are needed to elucidate specific causes and subgroups of women at risk.

The present study is the first to quantify menopausal complaints in autistic women. In agreement with previous qualitative studies (Moseley et al. 2020b, 2020a), we found that autistic women experience more menopausal complaints. Autistic women reported higher levels of total complaints, which was related to higher psychological and somatic menopausal complaints compared to non-autistic women, but not to higher urogenital complaints. Menopausal complaints are thought to be caused by highly irregular fluctuations in estrogens (Nelson 2008). Previous studies have suggested that the hormonal balance is different in autistic women (e.g., Gasser et al., 2020; Ingudomnukul et al., 2007; Pohl et al., 2014), which could cause the increase in menopausal complaints in autistic women. A different, but likely complementary, explanation is that autistic women are more sensitive to changes in their body that occur during (peri) menopause due to an overall increased sensory sensitivity (Acevedo et al. 2018; Schauder and Bennetto 2016). This may also possibly suggest that autistic women may experience menopausal complaints sooner than non-autistic women and might experience them for a longer period of time. Interestingly, also in ADHD increased menopausal complaints are noted (Dorani et al. 2021), suggesting that perhaps neurodiversity and its underlying etiology is also associated with increased difficulties during this transitional period. This could indicate that for example the interplay between neurotransmitters and sex (for example see Frey & Dias, 2014) might also play a part in the relation between neurodiversity and menopausal complaints. The interplay between hormonal levels, neurodiversity, and sensory sensitivity in the experience of menopause is currently unknown. While there is an obvious need for such studies, the methods used for the measurement of estrogen levels lack accuracy and precision when concentrations are lower as in menopause (Rosner et al. 2013). Careful thought and consideration have to be put into designing such studies.

Menopause is often associated with increased levels of depression and anxiety. Indeed, next to increases in psychological complaints related to menopause, our results also indicate that increased psychological menopausal complaints were associated with depressive symptoms. More surprising is the positive association between characteristics of ADHD (inattention and hyperactivity/impulsivity) and menopausal complaints in non-autistic women, which we did not detect in autistic women. Moreover, we also detected an increase in autistic characteristics associated with psychological menopausal complaints in autistic women. Clinically this finding of increased psychological complaints during menopause is of major significance, as women might

seek help for these problems. Moreover, characteristics of ASC or ADHD in this period might require a different clinical approach. Especially the relationship between menopausal complaints and ASC and ADHD characteristics is of interest as we do not know whether or not these characteristics are transient (i.e., disappear after the menopause). Knowing whether these are transient or not, will impact both ASC and ADHD assessment during this hormonal phase. Moreover, we do not know whether evidence-based interventions will be equally effective during menopause. The relationship of ASC characteristics with menopausal complaints in autistic women specifically fits well with the idea that autistic women could be able to mask their autistic characteristics until they reach menopause as also indicated in (Moseley et al. 2020b).

The current study is the first to quantitatively assess menopausal complaints in ASC. However, the results should be seen in the light of some limitations. We did not have any information about hormone therapy, often used to control symptoms of menopause (Steward et al. 2018). If either autistic or non-autistic women have less access to such treatments, this could have biased our results. Second, menopausal complaints change considerably over time. Unfortunately, we did not have the opportunity to investigate such patterns, and whether such patterns are different in autistic and non-autistic women. To accurately perform such a study, one would need large and importantly longitudinal samples. Lastly, we used the AQ to quantify autistic characteristics. Previous studies have emphasized the male biases in ASC measures (Lai et al. 2015), and that women might meet diagnostic criteria in a different manner than men do.

In conclusion, we show increased menopausal complaints in autistic women. Moreover, we found that menopausal complaints were associated with increased levels of psychological/psychiatric symptoms. In contrast with previous work did not find an increased prevalence of PMDD in autistic women. With this work, we show the important role that major reproductive milestones can have in an autistic woman's life. Increasing knowledge about the causes and impact of hormonal changes is of major importance, to provide women with the support that they require in every life phase.

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Table 1. Participant characteristics

PMDD						
	Autism (n=28)		Comparisons (n=42)			
	m(SD)	min-max	m(SD)	min-max	t	p-value
Age	49.8 (14)	31-72	56.2 (15.4)	31-79	-1.80	0.08
Gender (F/M/O)	28/0/0		42/0/0			
AQ	37.7 (6.7)	22-48	12.3 (5)	3-27	17.21	<.001
IQ	114.7 (15.4)	85-144	111.6 (18)	73-137	0.78	0.44
MMSE	29.5 (.6)	28-30	29.2 (.9)	27-30	1.71	0.09
Education ^a	1/0/0/0/5/10/15		0/0/0/0/6/21/15			.33
Menopause						
	Autism (n=30)		Comparisons (n=35)			
	m (SD)	min-max	m(SD)	min-max	t	p-value
Age	58.5 (8.8)	42-73	62.9 (9.2)	45-79	-1.95	0.06
Gender (F/M/O)	30/0/0		35/0/0			
AQ	35.1 (6.6)	24-48	12.3 (5.3)	3-27	15.14	<.001
IQ	116.8 (14.6)	92-144	119.1(13.3)	85-137	-0.66	0.51
MMSE	29.2 (0.9)	27-30	29.2 (0.7)	28-30	-0.29	0.78
MRS total	14.1 (6.8)	3-33	6.42(4.3)	0-17	5.28	<.001
- Somatic	6.0 (2.7)	2-13	2.8 (2.1)	0-8	5.26	<.001
- Psychological	5.2 (3.1)	0-10	1.7 (2.0)	0-7	5.28	<.001
- Urogenital	2.7 (3.2)	0-10	1.7 (2.0)	0-9	1.43	0.16
Education ^a	1/0/0/1/6/12/10		0/0/0/0/6/18/11			.56

Note. AQ-autism quotient, IQ – intelligence quotient, MMSE- mini mental state examination, MRS- menopause rating scale F/M/o= female/male/other. ^aeducation ranges from 1 (primary education not finished) to 7 (university level degree based on the Verhage coding system (1964)). For statistical testing education levels were merged to prevent empty cells

Table 2. Relation between psychological symptoms and menopausal symptoms

Menopausal complaints								
ASC								
	Total		Psychological		Somatic		Urogenital	
	r	p	r	p	r	p	r	p
Anxiety	0.16	.25	0.13	.05	0.01	.53	0.00	.79
Depression	0.26	.01	0.31	.001	0.03	.38	0.07	.16
Total AQ	0.09	.07	0.21	.01	0.01	.70	0.04	.32
ADHD- IN	0.15	.73	0.00	.83	0.00	.71	0.00	.93
ADHD- H/I	0.15	.75	0.03	.32	0.01	.52	0.06	.20
Comparisons								
	Total		Psychological		Somatic		Urogenital	
	r	p	r	p	r	p	r	p
Anxiety	0.12	.04	0.16	.02*	0.00	.99	0.00	.87
Depression	0.07	.12	0.26	.002	0.06	.15	0.00	.99
Total AQ	0.07	.14	0.09	.08	0.06	.14	0.00	.98
ADHD- IN	0.17	.01	0.15	.02*	0.02	.46	0.06	.15
ADHD- H/I	0.24	.003	0.15	.02*	0.08	.10	0.09	.08

Note. ADHD- Attention-deficit/ hyperactivity disorder, AQ-autism quotient, ASC- autism spectrum conditions, H/I- hyperactivity impulsivity, IN- inattention. Bolded figures are significant after correction for multiple comparisons. * not significant after multiple testing correction.

Figure 1. Density plot of total menopausal complaints.

Note. Dotted vertical lines indicate group means.

Figure 2. Relations between total menopausal complaints and psychiatric symptoms

Note. Stars indicate significant relationships at $p < .01$.