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Title page

Normative Bladder Diary Measurements in Pregnant Women.

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Condensation

Bladder diaries in pregnant women revealed smaller bladder capacity and total voided volume, maintaining normal voiding frequency with no statistically significant difference across trimesters.

ABSTRACT

Objective: Studies have demonstrated a strong positive correlation between bladder capacity and total volume voided in asymptomatic non-pregnant women. Therefore, to adequately characterise the normative data, it was important to compare bladder capacity vs. 24-hour volume (V_{24}) relationships in our pregnant study population.

Our objectives were to (1) collect normative bladder diary measurements from asymptomatic primigravid women, (2) investigate the relationship between these measurements and gestation of pregnancy, and (3) compare these normative measurements from pregnant women with those from asymptomatic non-pregnant women. We focused on measures of “bladder capacity” [average (“V_{avg}”) and maximum volume per void (“V_{max}”)], (“V_{24}”), and voiding frequency (“F_{24}”).

Study Design: Three-day bladder diaries were collected from 41 primigravid women, one three-day diary per trimester. We compared our pregnant data with non-pregnant data previously collected by Amundsen et al using identical methods. Relationship between variables analysed using the Kruskal-Wallace and Mann-Whitney tests.

Results:

We found no significant differences across trimesters among bladder diary measurements (p-values: F_{24} = 0.711; V_{max} = 0.912; V_{avg} = 0.894, and V_{24} = 0.675).

A comparison between pregnant and non-pregnant data showed no significant difference between F_{24}, but a significantly lower V_{24}, V_{avg} and V_{max} in pregnant women. Regression analysis showed no significant differences between the pregnant and non-pregnant, V_{24} vs. bladder capacity relationships.

Conclusions: Pregnancy results in smaller bladder capacities and lower V_{24}, with a normal relationship between V_{24} and bladder capacity, maintaining normal voiding frequency. We used our data to construct a nomogram to help clinicians compare the relative contributions of increased V_{24} and reduced bladder capacity to increased F_{24}.

INTRODUCTION

Studies have demonstrated a positive correlation between bladder capacity and total volume voided in asymptomatic non-pregnant women[1,2]. Thus, for example, based on the findings of Amundsen, et al [2] a 25 year old woman's average voided volume (V_{avg}) of 200 ml would be in the ^{64th} percentile (normal) if her 24-hour volume (V_{24}) were 1,000 ml but would be below the 1st normative percentile (abnormal) if her V_{24} were 2,500 ml. Therefore, to adequately characterise the normative data, it was necessary to compare bladder capacity vs. V_{24} relationships in pregnant and non-pregnant women. Our study's objective was to obtain normative bladder diary measurements to assist in the management of pregnant women when they present with lower urinary tract symptoms (LUTS). The study focused on V_{24}, V_{avg} and maximum volume per void (V_{max}) [$V_{avg,}$ and V_{max} – being measures of "bladder capacity"] and voiding frequency (F_{24}). Our study also included an investigation of the effects of gestation on these measurements.

MATERIALS AND METHODS

Ethics approval was obtained from the NRES Committee London and research and development department at Birmingham Women's NHS Foundation Trust, Birmingham, UK.

Pregnant women were selected under the following eligibility requirements:

- Primigravida women - age limit 16 to 40 years
- Self-declared absence of lower urinary tract symptoms via a standardised questionnaire[3] (See Supporting Information)
- Fully understood, and consented to the study.

Potential subjects were approached in the antenatal clinic and provided with the study information. If they agreed to participate, written consent was obtained after a viable first trimester pregnancy was diagnosed on ultrasound scan. Three "bladder diary kits" were provided, one for each trimester. The kits consisted of diary forms, a 1-ltr capacity measuring vessel graduated in 25ml increments, and two self-addressed and stamped envelopes to return the diaries. The first bladder diary was to be completed as soon as possible, and returned to the hospital at the mid-trimester scan appointment. The second and third bladder diaries were to be returned to the hospital in the envelopes provided. Study participants were sent reminders via email and telephone at regular intervals to complete and return the diaries.

Subjects were excluded if (1) The standardised questionnaire revealed bladder symptoms, previous urological or continence surgery, medications influencing bladder habits or a night-shift sleep pattern and/or (2) Diaries contained one or more incontinence episodes in the first trimester of pregnancy.

We compared our normative pregnancy data with data from a previously published study that collected normative non-pregnant female bladder diary measurements[(4)]. The previous study's methods of subject selection, administration and analysis of the bladder diary were identical to our study. A subset of the non-pregnant population was extracted to age-match with our pregnant women.

A scannable bladder diary form was used in this study (See Supporting Information). To make the diary's wake up and bed times conform to ICS definitions[(5)], wake up is labelled "Start of Day", and is defined in the instructions as "when you leave your bed for the day," and "Bed Time" is defined as "when you turn the lights out in preparation for sleep." The diary allows for the possibility that subjects may be in a situation where measuring urine volume is awkward or impossible. To accommodate such omitted volume measurements, the diary provides a check box to indicate that a void occurred, but volume was not measured. When analysing the diary, the computer enters the median volume of all voids into such omitted volumes. The diary form also includes check boxes for recording incontinence episodes. Parsons et al [(6)] compared manual and computerised diary measurements of V_{24}, F_{24}, V_{avg}, and V_{max} in 50 asymptomatic women. Correlation coefficients ranged from 0.658 to 0.775, and all P values were less than 0.0001.

Completed diary forms were scanned into a computer, which extracted the data by intelligent character recognition. The handwriting recognition results were manually checked against the original form, and corrected as necessary. From each diary, V_{24}, F_{24}, V_{max} and V_{avg} were calculated for all voids recorded over the entire 3-day diary period (calculation methods summarised in Supporting Information).

Statistical Analysis

All analyses were performed using Minitab 15 or STATA12.1. Amongst differences between diary measurements, all of the studied variables failed the Anderson-Darling test for normal distribution. Therefore to test the significance of differences between medians, the non-parametric Kruskal-Wallace test was used for differences between trimesters and the Mann-Whitney test for pregnant versus non-pregnant differences.

For regression analysis, inspection of residual vs. V_{24} plots suggested linear relationships. Therefore, V_{avg} vs. V_{24} relationships were characterised by linear regression. Student's t test was used to test differences between regression intercepts and slopes and between variabilities as characterised by scatter about the regression line. The F test was used to test for differences between regression coefficients. A P value of less than 0.05 was designated as "significant". Missing data were handled by complete case analysis for all variables.

We constructed a V_{avg} vs. V_{24} nomogram from the regression results as follows:

1) We calculated the difference between each data point's actual value and its estimated value calculated by the regression equation (the data point's "residual value").
2) We calculated the residual values at the 5^{th}, 15^{th}, and 25^{th} percentiles and subtracted them from the regression equation to obtain the 5^{th}, 15^{th} and 25^{th} percentile lines (as shown in Figure 4 of Supporting Information).

RESULTS

During the period from April 2012 to January 2013, sixty-one pregnant women were recruited into the study. Three women opted out and four women were excluded due to the pregnancy ending in a miscarriage. Of the 54 remaining patients, 41 completed all three bladder diaries. 51% of our asymptomatic pregnant population was Caucasian; 31% were Asian (Indian, Pakistani, Srilankan, Bangladeshi); 12% were black, and 5% were oriental. The mean age of our pregnant subjects was 28.9 and median age was 29.0. 83% of the first trimester diaries were completed between 11-12 weeks; 95% of the second trimester diaries were completed between 13 – 24 weeks, and 90% of the third trimester diaries were completed by 36 weeks of gestation. (Supporting information- Table 1.)

Mean and median ages of the age-matched non-pregnant population were 29.3 and 30.2 years respectively. Of these 75.8% were Caucasian; 15.5% were Black; 2.4% were Asian, and 2.5% were other ethnic groups. Figure 1 presents boxplots showing our bladder diary measurements' distributions across trimesters. The upper and lower boundaries of the "boxes" are the 25th and 75th quartiles. The lines extend from the boxes 1.5 times the upper and lower 75th quartiles. The asterisks plot "outliers that are beyond 1.5 times the quartiles. That all outliers are in the positive direction is a manifestation of the data's rightward skew. P values yielded by Kruskal-Wallis tests of differences among trimesters are shown to the right of each set of plots. There are clearly no significant differences across trimester among bladder diary measurements from our pregnant population.

Figure 2 presents boxplots comparing day, night, and 24-hour frequencies and volumes (F_{day}, F_{nt}, F_{24}, V_{day}, V_{nt}, V_{24}) and bladder capacities (V_{max} and V_{avg}) from pregnant (second trimester data) and non-pregnant women. Results of Mann-Whitney tests of pregnant vs. non-pregnant measurements are shown to the right of the boxplots. Both bladder capacity and total volume are significantly smaller in the pregnant women (all P values are less than 0.000). However, there are no significant differences between voiding frequencies (p value = 0.2 to 0.8).

Figure 3 shows superimposed V_{avg} vs. V_{24} scatter plots and regression lines of non-pregnant and second trimester pregnant data. (The first and third trimester plots show similar results.) The regression lines do not appear to differ significantly suggesting that the V_{avg} vs. V_{24} relationship is normal in pregnancy. However, the pregnancy data points concentrate in the lower end of the V_{24} range – reflecting the decreased median V_{24} shown by the box-plots. Thus, the data suggest that pregnancy tends to decrease bladder capacity and 24-hour urine production but does not affect the V_{24}-V_{avg} relationship.

Table 1. presents tests of the significance of differences between regression parameters among the subject groups. There are no significant differences among trimesters (e.g., P values of Intercept differences were as follows: Tri-1 vs. Tri-2 = 0.70; Tri-1 vs Tri-3 = 0.40; Tri-2 vs. Tri-3 = 0.80.) and between pregnant and non-pregnant regression parameters. This supports the conclusion from inspection of the scatter plots that the V_{24} vs. V_{avg} relationship in our pregnant women did not differ significantly from asymptomatic non-pregnant women. However, the correlation coefficients were significantly higher in our pregnant groups (P = 0.01 – 0.04). This is probably a reflection of the higher variability of the non-pregnant measurements (P- <0.000 – 0.006).

COMMENTS

It is widely recognised that lower urinary tract symptoms (LUTS) are more common in pregnant women than in non-pregnant women.[7] Therefore, management of LUTS is equally important in the pregnant population. Our normative data may support the management of this group of patients by helping the clinician sort out the relative contributions of increased voided volume and decreased bladder capacity to an increase in voiding frequency.

Many clinicians might have the pre-conceived concept that urinary frequency increases as the enlarging uterus compresses the bladder. On the contrary our results suggest that, although bladder capacity is decreased in asymptomatic pregnant women, a decrease in total volume voided, tends to keep voiding frequency normal. Figure 4 in Supporting Information presents a nomogram that can be used to compare the V_{24} and V_{avg} percentiles within our asymptomatic population. High voided volume would be more likely to contribute to a patient's high voiding frequency if her V_{24} were over the 95th percentile (example data point "B" in Fig. 4) than would a patient with V_{24} at the 60th percentile (example data point at "A" in Fig. 4 in Supporting Information).

Table 2. compares bladder diary variables from our study of pregnant women with previously published studies from non-pregnant women[4,8,9,10,11]. Except for some Homma, et al[10] outliers (V_{24} vs. Tri-3, and all V_{avg} and V_{max} measurements), the previously published results support our finding that asymptomatic pregnant women have smaller bladder capacities and lower total voided volumes than asymptomatic non-pregnant women.

We found that 24-hour urine production is decreased in pregnancy. Two possible mechanisms could have contributed to this decrease: (1) decreased water intake and (2) increased total body water (TBW) retention. Analysis of the within-trimester diary completion times revealed that 83% of our first trimester diaries were completed late in the trimester (11-12 weeks). Human and animal studies [12] suggest that in pregnancy TBW accretion increases until about 8 weeks after gestation, at which time accretion stops with TBW having increased 7-8 litres (L). Thus, published data are compatible with a hypothetical V_{24} increase early in pregnancy. Our trimester data suggest a flat V_{24} for the remainder of the pregnancy.

However, our pregnant V_{24} values are 649 ml less than our non-pregnant V_{24} values (Figs 1 and 2). This would produce a total volume voided decrease of 36 liters over 8-11 weeks – well outside the possibility that TBW accretion accounts for all of the decreased urine output. However, the assumption that decreased water intake accounts for the rest of the V_{24} decrease encounters difficulty because of minimal and conflicting published data that are available.[13,14] A future voiding diary study in pregnancy that includes intake diaries might help resolve this dilemma.

Strengths

As far as we know, ours is the first study that presents normative bladder diary measurements in the pregnant population. It also compares data for all three trimesters of pregnancy, and investigates the effect of pregnancy on the total volume voided vs. bladder capacity relationship.

Limitations

In our study we did not collect fluid intake data, which might have helped explain the reduced 24-hr urine production values. The non-pregnant normative data were collected by four different study sites versus the single-site source for our pregnant data. This may have caused the increased variability and lower correlation of our non-pregnant bladder capacity vs. total volume voided relationship. However, it is also possible that the reduced variability of the pregnant data is a manifestation of the fact that the pregnant data tend to concentrate at lower total volumes than the non-pregnant data.

Our data are limited to primigravid women. A study including multiparous women may have increased the clinical utility of our study.

We present our data in the form of a nomogram designed to allow comparison of relative degrees of "abnormality" (percentiles within our asymptomatic population) of V_{24} and bladder capacity (V_{avg}). This nomogram is presented only as an illustration of the possible clinical application of our data. It is preliminary and, if used, should be used cautiously and only with the full understanding that its utility needs to be validated by a study of its application to symptomatic pregnant patients.

CONCLUSIONS

In asymptomatic nulliparous pregnant women, we found no significant differences between bladder capacity or total volume voided across trimesters. Compared to asymptomatic non-pregnant women, pregnancy tends to decrease V_{24} and bladder capacity. Our inter-trimester time course analysis suggests that most of this V_{24} decrease occurs during the first 11 weeks of pregnancy and the V_{24} trend remains flat for the remainder of the pregnancy.

We also found that between our patients and non-pregnant subjects there was no significant difference in the V_{24} vs. bladder capacity relationship and voiding frequency – a reflection of the normal bladder capacity vs. V_{24} relationship in pregnant women. These results suggest that, when managing pregnant women with increased voiding frequency, causes other than just the pregnancy should be investigated. To illustrate its potential clinical application, our normative data are presented in the form of a nomogram designed to help the clinician compare the relative contributions of increased V_{24} and decreased bladder capacity to the increased voiding frequency.

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1. Dr Fidan Israfilbayli.
   Senior Registrar Obstetrics and Gynaecology
   We acknowledge her help in the ethics application process for the study.

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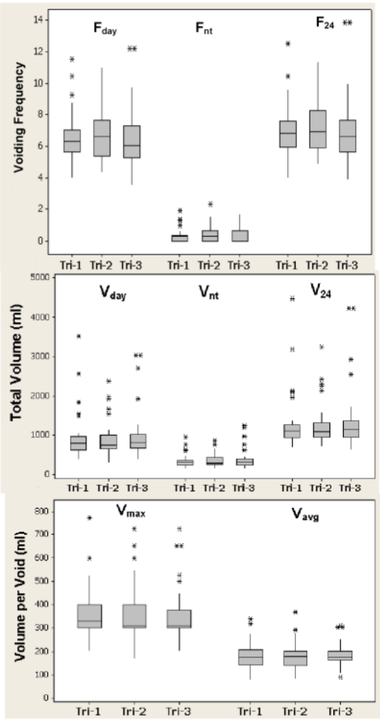
Figure Legends

Fig. 1. Boxplots of bladder diary measurements by trimester. The upper and lower boundaries of the “boxes” are the 25th and 75th quartiles. The lines extend from the boxes 1.5 times the upper and lower 75th quartiles. The asterisks plot “outliers that are beyond 1.5 times the quartiles. That all outliers are in the positive direction is a manifestation of the data’s rightward skew. The results of Kruskal Wallace tests are presented to the right of the boxplots.



Significance of Differences (P)

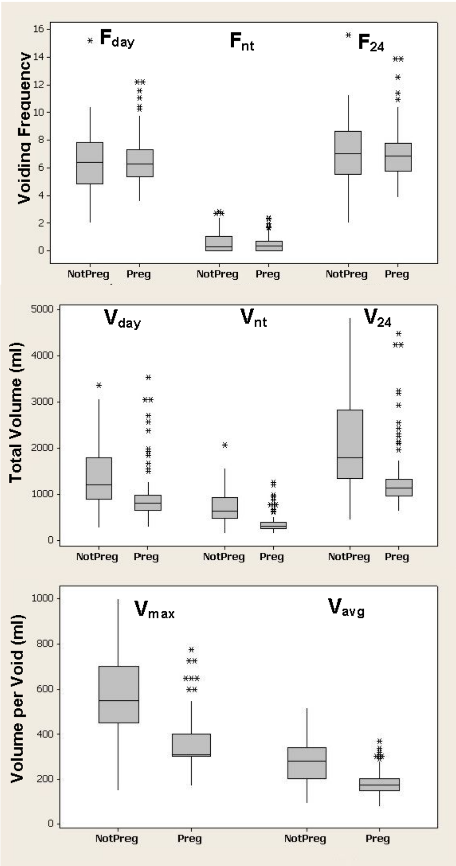
	Medians Tri-1	Tri-2	Tri-3	P
F_{day}	6.30	6.60	6.03	0.87
F_{nt}	0.33	0.33	0.00	0.87
F_{24}	6.84	6.93	6.60	0.71

	Medians Tri-1	Tri-2	Tri-3	P
V_{day}	798	738	811	0.70
V_{nt}	304	292	302	0.97
V_{24}	1103	1097	1136	0.68

	Medians Tri-1	Tri-2	Tri-3	P
V_{max}	330	310	310	0.91
V_{avg}	174	178	174	0.89

Fig 1 – Boxplots of bladder diary measurements by trimester.

Fig. 2. Boxplots comparing bladder diary measurements in pregnant and age-matched non-pregnant women. Significance of pregnant (2nd trimester) vs. non-pregnant differences were tested with the Mann-Whitney test. Results are shown to the right of the graphs. See Fig. 1 caption for boxplot presentation conventions.



Significance of Differences (P)

	Medians		
	Preg	**N Preg**	**P**
F_{day}	6.3	6.4	0.798
F_{nt}	0.3	0.3	0.207
F_{24}	6.8	7.0	0.662

	Medians		
	Preg	**N Preg**	**P**
V_{day}	798	1192	0.000
V_{nt}	297	624	0.000
V_{24}	1129	1778	0.000

	Medians		
	Preg	**N Preg**	**P**
V_{max}	310	550	0.000
V_{avg}	174	279	0.000

Fig 2 – Boxplots comparing bladder diary measurements in pregnant and age-matched non-pregnant women.

Fig. 3. Superimposed V_{avg} vs. V_{24} scatter plots with results of linear regression. Linear regression equations are shown at bottom right (blue = pregnant; red = non-pregnant). The second trimester is shown as representative of the other two trimesters (Regression results did not differ significantly across trimesters – see Table I.) Solid lines plot the 50th percentile, and the red dashed lines plot the 5th and 95th percentiles of the non-pregnant population.

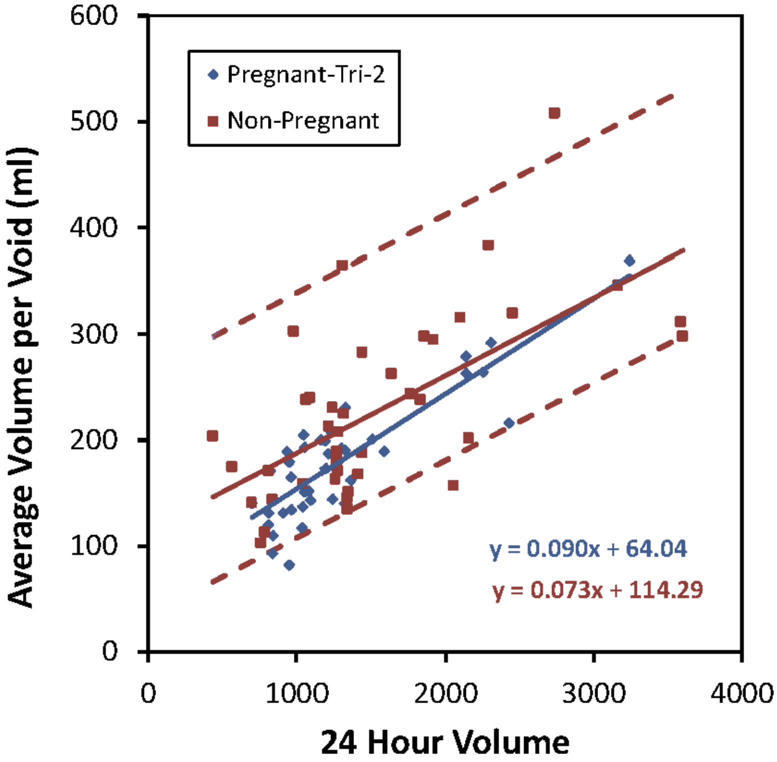


Fig 3 – Superimposed Vavg vs. V24 scatter plots with results of linear regression.

Table 1. Comparison of Regression Results

		β_0	**Significance of Differences**		
	NP	114.3	**P**		
Intercepts	**T1**	98.7	**Vs. NP**		
(t test)	**T2**	64.0	0.60	**Vs. Tri-1**	
	T3	116.3	0.09	0.70	**Vs. Tri-2**
			0.95	0.40	0.80
		β_1	**P**		
	NP	0.073	**Vs. NP**		
Slopes	**T1**	0.064	0.60	**Vs. Tri-1**	
(t test)	**T2**	0.090	0.40	0.70	**Vs. Tri-1**
	T3	0.050	0.19	0.50	0.50
		R^2	**P**		
	NP	0.395	**Vs. NP**		
Correlations	**T1**	0.617	0.04	**Vs. Tri-1**	
(F test)	**T2**	0.725	0.01	0.3	**Vs. Tri-1**
	T3	0.672	0.04	0.4	0.4
		Mean	**P**		
Variability	**NP**	45.6	**Vs. NP**		
(t test on	**T1**	25.9	0.006	**Vs. Tri-1**	
residuals)	**T2**	20.7	0.000	0.186	**Vs. Tri-1**
	T3	17.7	0.000	0.041	0.452

Table 2: Comparison of studies with non-pregnant and pregnant data

	Larsson and Victor (1988) 2-day diary	Kassis and Schick (1993) 7-day diary	Homma et al (2000) 1-day diary	Fitzgerald et al (2002) 1-day diary	Amundsen et al (2007) 3-day diary	This study 3-day diary
Subjects (No.)	151	33	32	300	161	41
V24 Mean (SD)	1430 (487)	1473 (386)	1332 (59)	1759 (797)	1730 (721)	I Tr 1212 (515.77) II Tr 1233 (644.04) III Tr 1341 (692.10)
F24 Mean (n ± SD)	5.8 (1.4)	5.6 (1.3)	8 (0.4)	8.3 (2.4)	7.1 (1.9)	I Tr 6.88 (1.71) II Tr 7.63 (1.61) III Tr 7.28 (1.94)
V_{avg} (mL ± SD)	250 (79)	__	175 (8)	216 (87)	245 (91)	I Tr 175.41 (52.35) II Tr 182.66 (55.3) III Tr 180.29 (54.33)
V_{max} (mL ± SD)	460 (174)	__	277 (16)	362 (161)	514 (190)	I Tr 349.14 (105.81) II Tr 354.39 (116.55) III Tr 347.80 (108.40)

SD, standard deviation; __, not reported. V24- Volume voided per 24 hours. F24- Frequency per 24 hours. Tr- Trimester