Title
Baseline Rates of Prior Pregnancy Differ for Meningioma, Cholelithiasis, and Trauma Patients: Gauging the population impact of pregnancy on hospital presentation for meningioma resection

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Baseline Rates of Prior Pregnancy Differ for Meningioma, Cholelithiasis, and Trauma Patients: Gauging the population impact of pregnancy on hospital presentation for meningioma resection.

Introduction

Meningioma specimens express progesterone receptors, and in vitro results suggest that exposure to these hormones facilitates meningioma growth[1,2]. While the pertinence of these observations to clinical practice remains unclear, several clinical findings support the role of progesterone in meningioma growth. The gender distribution of meningioma incidence is skewed towards women during peak reproductive years when systemic progesterone levels are highest[2]. Additionally, case reports also show meningiomas become symptomatic during late stages of pregnancy[3,4] and shortly before menstruation[5], which represent periods of high progesterone. Furthermore, women receiving hormone replacement therapy [5], oral contraceptives[5], or with a prior history of uterine leiomyoma[12] are at a higher risk of meningioma.

However, a number of studies also dispute the clinical significance of progesterone in meningioma incidence. Histological analysis of some meningiomas resected during pregnancy have revealed predominantly vasogenic as opposed to hormone-driven tumor growth[7,8]. Furthermore, a phase III clinical trial of progesterone antagonist mifepristone failed to show significant improvement in median progression-free survival compared to placebo in meningioma patients[9]. A large, European cohort study has also failed to find any association between meningioma risk and reproductive factors such as age at menarche, parity, age at first birth, menopausal status, and age at menopause[6].

The purpose of this study is to evaluate the relationship between pregnancy and meningioma progression, using the surrogate measure of hospital admission for meningioma resection. If progesterone plays a clinically significant role in the pathogenesis of meningioma, then exposure to high doses of progesterone during pregnancy may increase the growth of an existing, subclinical meningioma causing it to become symptomatic. To investigate whether such a pattern can be observed, we calculated the baseline rates of prior pregnancy in three different populations to better understand whether pregnancy was associated with meningioma resection. We report hazard ratios for recent pregnancy as a risk factor for these conditions.

Methods

The data source for this study was the California Office of Statewide Health Planning & Development (OSHPD) longitudinal inpatient-discharge administrative database for the years 1995 to 2010, obtained from the State of California Office of Statewide Health Planning & Development (State of California Office of Statewide Health Planning & Development. Healthcare information division: Patient discharge data. http://www.oshpd.ca.gov/HID/Products/PatDischargeData/PublicDataSet/index.html. Updated 2012. Accessed 8/21, 2012). The California inpatient discharge database is an administrative, longitudinal database that represents a 100% sample of all inpatient discharges from California licensed hospitals. Each patient within the database is given a unique, masked patient identifier so that each patient may be followed throughout multiple inpatient hospital stays, across multiple institutions, and over multiple years within the state of California during the study period.

Due to the low incidence of meningiomas in the general population, a case-control rather than a cohort design was chosen for this study. This increases the power of the study by utilizing the maximum sample size of meningioma patients to avoid type II error.

Inclusion Criteria

Patients were selected based on *International Classification of Diseases*, 9th revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes. Female patients were included as cases in this study if they were given both a diagnosis code of meningioma and also a procedure code for resection of the mass during the same hospital admission. Due to the use of an inpatient database, it was not possible to select a control group from the general population. Therefore, this study compared meningioma patients to trauma patients and cholelithiasis patients as controls. Trauma patients were utilized as a negative control because there currently exists no evidence for a correlation between a prior pregnancy and trauma incidence in an inpatient setting. Conversely, gallbladder disease is cited as a common non-obstetrical cause of maternal hospitalization in the first year post-partum[10,11]. Cholelithiasis patients were therefore chosen as a positive control population due to the well-documented positive association of pregnancy with cholelithiasis incidence. Frequency matching was used to compile age-matched control groups of female trauma and cholelithiasis patients were arranged with meningioma resection cases in a 3:1 case-control fashion.

Exclusion Criteria

Patients that received a hysterectomy, bilateral oophorectomy, or bilateral salpingectomy before their meningioma resection were excluded. Patients that had a concurrent trauma and meningioma diagnosis were also excluded to ensure separation between the case and negative control groups. To capture patients of childbearing age, patients under 14 or over 55 years of age were also excluded. All patients diagnosed with meningioma, trauma, or cholelithiasis before the year 2000 were also excluded to allow for a 5-year washout period ensuring that only first-time meningioma resections were captured.

Patient Exposure

The primary exposure examined in this study was pregnancy defined as live-birth or still-birth at full term. This definition was chosen to ensure roughly equal exposure time to progesterone among all patients when referencing their most recent pregnancy. We specified the outcome by defining it as an admission with a diagnosis of normal delivery, or an admission with a delivery-related diagnosis and a concurrent, delivery-related obstetrical procedure.

Analysis: All analysis was performed on Stata 11.2. Statistical significance was determined at $p \leq .05$. A Kaplan-Meier plot and cumulative survival estimates were used to analyze the incidence of cumulative prior pregnancy starting at 1 year before hospital admission for either meningioma resection, cholelithiasis, or trauma. . Censoring events were the date of birth and January 1, 1995, which is the earliest date in the database. A Cox proportional hazards regression was also carried out for the year preceding hospital admission adjusting for patient, race, comorbidities (based on the Charlson index), and insurance status. As this study utilizes age-matched groups, age was not adjusted for in the cox proportional hazards regression.

Results:

This study included 2,613 meningioma patients. 3:1 Age-matched groups of trauma and cholelithiasis patients were included, amounting to a total of 18,291 patients. Of these, 2,636 (14.4%) patients had pregnancies after January 1, 1995 that were captured by the database. The majority of patients were Caucasian, had private insurance, and had a Charlson index ≥2. The median age at meningioma resection was 46 years and the first and third quartiles were 41 years and 51 years, respectively (table 1).

Table 1: Characteristics of the Study Population

	Patients	**%**
Diagnosis		
Meningioma	2,613	14.29
Trauma	7,839	42.86
Cholelithiasis	7,839	42.86
Prior Pregnancy		
Yes	2,636	14.41
No	15,655	85.59
Race		
Caucasian	10,335	57.07
African American	1,492	8.24
Hispanic	4,613	25.47
Asian	1,125	6.21
Native American or Other	543	3.00
Insurance Status		
Uninsured	1,175	7.08
Medi-Cal	3,508	21.13
Medicare	1,077	6.49
Private Insurance	10,842	65.31
Charlson Index		

0	8,357	45.69
1	1,450	7.93
≥2	8,484	46.38
Age		
Range	14-55	
25%ile	41	
Median	46	
75%ile	51	

Kaplan-Meier curves demonstrated significantly higher cumulative rates of pregnancy among patients admitted for meningioma resection compared to trauma patients over 1 year prior to each respective admission. Significantly higher cumulative rates of prior pregnancy were also detected in cholelithiasis patients compared to both meningioma and trauma patients over 1 year prior to admission (figure 1).

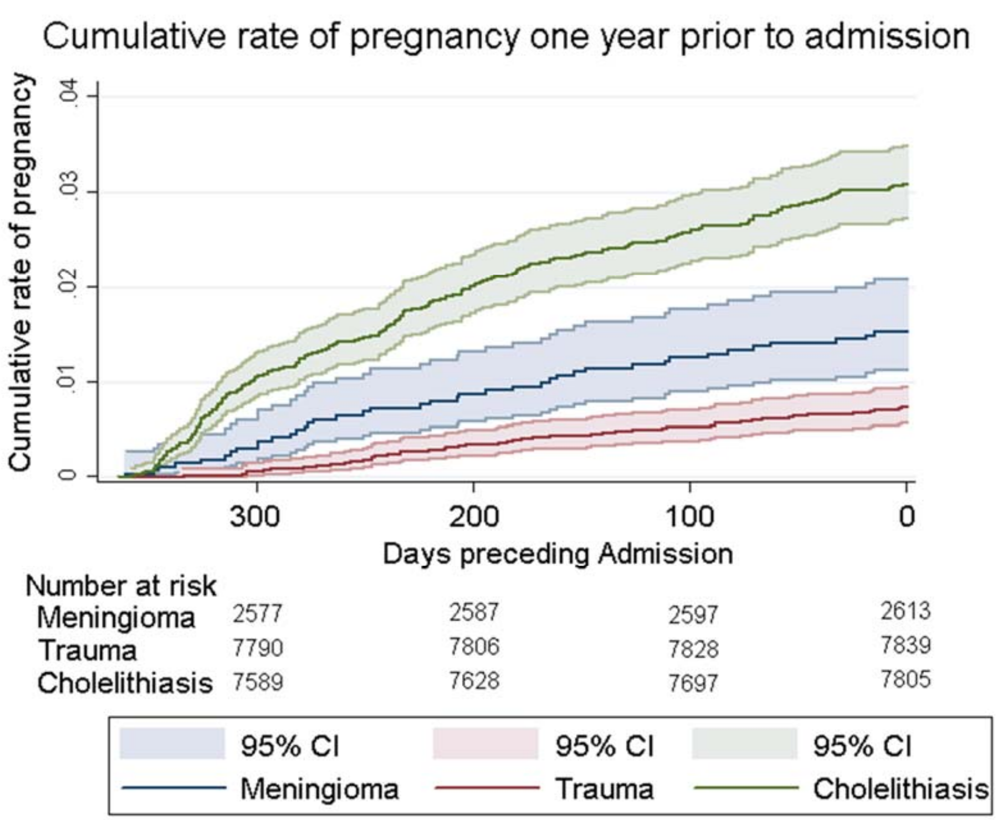

Figure 1:Kaplan–Meier graph of the cumulative pregnancy rates preceding hospital admission

By the time of admission, 1.53% (95% CI: 1.13%-2.08%) of patients admitted for meningioma resection had experienced a pregnancy within the previous year compared to 0.74% (95% CI: 0.57%-0.96%) of trauma patients and 3.09% (95% CI: 2.73%-3.50%) of cholelithiasis patients (Table 2).

Table 2: Cumulative survival estimates of pregnancy rates preceding hospital admission

Cumulative Pregnancy Rates	**Trauma**		**Meningioma**		**Cholelithiasis**	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
11 months preceding admission	0.0001	0.0000 - 0.0009	0.0015	0.0006 - 0.0041	0.0036	0.0025 - 0.0053
6 months preceding admission	0.0040	0.0028 - 0.0056	0.0096	0.0065 - 0.0141	0.0215	0.0185 - 0.0250
Immediately preceding admission	0.0074	0.0057 - 0.0096	0.0153	0.0113 - 0.0208	0.0309	0.0273 - 0.0350

The differences observed in the Kaplan Meyer graph and survival estimates does not take into account differences in demographics and comorbidities among the three populations, which may confound the result. Therefore, a bivariate analysis was undertaken to investigate differences that were statistically significant. Significant differences were detected between the cholelithiasis, meningioma, and trauma populations in terms of race, insurance status, and comorbidities, as measured by the Charlson index (table 3).

Table 3: Characteristics of trauma, cholelithiasis, and meningioma patients

	Trauma	**%**	**Cholelithiasis**	**%**	**Meningioma**	**%**	**p-Value**
Prior Pregnancy							
Yes	899	11.47	1,362	17.37	375	14.35	< .001
No	6,940	88.53	6,477	82.63	2,238	85.65	
Race							
Caucasian	4,938	63.80	3,889	49.99	1,508	58.27	< .001
African American	708	9.15	591	7.60	193	7.46	
Hispanic	1,450	18.73	2,652	34.09	511	19.74	
Asian	388	5.01	439	5.64	298	11.51	
Native American or Other	256	3.31	209	2.69	78	3.01	
Insurance Status							
Uninsured	678	10.01	448	6.11	49	1.97	< .001
Medi-Cal	1,405	20.73	1,725	23.52	378	15.17	
Medicare	571	8.43	397	5.41	109	4.37	
Private Insurance	4,122	60.83	4,764	64.96	1,956	78.49	
Charlson Index							
0	6,308	80.47	<10	<0.13	2,042	78.15	< .001
1	1,074	13.70	<10	<0.13	369	14.12	

≥2	457	5.83	7,825	99.82	202	7.73	
Age							
Mean	44.9		44.9		44.9		1
95% CI	44.6-45.2		44.7-45.1		44.7-45.1		

In order to address the issue of confounding variables, significant factors were adjusted for in a Cox proportional hazards regression. This analysis demonstrated statistically significant increased rates of prior pregnancy in meningioma patients compared to trauma patients (HR 1.86, 95% CI: 1.22-2.83). Patients diagnosed with cholelithiasis had higher rates of preceding pregnancy compared to both meningioma and trauma patients (HR 6.26, 95% CI 2.35-16.66) (table 4).

Table 4: Multivariate predictors of pregnancy one year preceding hospital admission

	HR	**95% CI**			**p-Value**
Diagnosis					
Trauma	Ref	Ref		Ref	Ref
Meningioma	1.86	1.22	-	2.83	**.004**
Cholelithiasis	6.26	2.35	-	16.66	**< .001**
Race					
Caucasian	Ref	Ref		Ref	Ref
African American	1.54	1.03	-	2.32	**.038**
Hispanic	1.84	1.43	-	2.36	**< .001**
Asian	1.55	1.01	-	2.38	**.045**
Native American or Other	0.85	0.38	-	1.93	.703
Insurance Status					
Uninsured	Ref	Ref		Ref	Ref
Medi-Cal	5.86	2.39	-	14.40	**< .001**
Medicare	0.22	0.03	-	1.92	.173
Private Insurance	4.38	1.80	-	10.65	**.001**
Charlson Index					
0	Ref	Ref		Ref	Ref
1	0.47	0.22	-	1.03	.059
≥2	0.53	0.20	-	1.41	.207

Discussion:

Past studies investigating the link between pregnancy and meningioma risk have yielded conflicting results. While one study identified a lower risk of meningioma with earlier age of first pregnancy and increased number of pregnancies[12], several studies have failed to reproduce this link and found either no significant correlation[13] or increased risk of meningioma in multiparous compared to nulliparous women[14]. While most studies have focused on the age of first birth and number of births as risk factors for meningioma, this study focuses on whether a patient undergoing meningioma resection was more likely to have had a recent pregnancy compared to other conditions and investigated the latency between the most recent preceding pregnancy and meningioma resection. This latency was analyzed by examining the relative rates of pregnancy in the year preceding meningioma resection compared to two other populations: trauma patients and cholelithiasis patients.

Trauma patients were chosen for comparison because pregnancy is not known to be a risk factor (and, in fact may be protective, in that pregnant patients may avoid trauma associated behaviors).Cholelithiasis patients were chosen for comparison because pregnancy is a known risk factor for cholelithiasis. As expected, both Kaplan-Meier curves and Cox proportional hazards regression revealed a higher rate of prior pregnancy among cholelithiasis patients compared to trauma patients one year prior to hospital admission. This is consistent with current literature, which cites pregnancy as one of the risk factors for gallstone formation[15-17] especially in the first year post-partum[10,11].

The Kaplan Meier and hazard function reveal significantly higher rates of preceding pregnancy in meningioma patients compared to trauma patients (figure 1). Meningioma patients also exhibited significantly lower rates of preceding pregnancy compared to cholelithiasis patients (figure 1). After adjusting for possible confounding factors in the Cox proportional hazards regression, these observed differences remained (table 4).

These findings indicate that patients admitted for resection of meningioma are more likely to have experienced a pregnancy in the year preceding their admission for resection, compared to trauma patients. However meningioma patients are less likely to have experienced a recent pregnancy compared to cholelithiasis patients. Therefore, these data suggest that the increased risk of a recent pregnancy on requiring a meningioma resection is less than its impact on cholelithiasis formation, which has been estimated at a relative risk of 2.4[17]. The results of this study support that pregnancy within the preceding year is a risk-factor for meningioma resection when using trauma patients as a control group. This may be due to pregnancy resulting in the expansion of an existing subclinical meningioma, causing it to become symptomatic and require resection. Therefore, patients with known meningioma who seek to become pregnant may be cautioned of this possible risk.

The strengths of this study lie in its longitudinal design and the utilization of a large, population based database. By utilizing data from all civilian hospitals in the state of California, this study was able to take advantage of a heterogenous population of 38 million inhabitants. This results in a heterogenous study with 3,989 female meningioma patients of childbearing age. The large sample size adds power and the heterogenous patient population makes this study relatively generalizable.

The major limitation of this study is its reliance on in-patient admissions. As such, control groups consisted of samples taken from the in-patient population and the trauma group may not be a representative of a true age matched 'normal' control group. However, as mentioned above, the differences between the trauma and cholelithiasis populations observed in this study agree with existing literature and allow us to gauge the relative impact of pregnancy on the likelihood of a patient requiring meningioma resection compared to two patient populations for which pregnancy has either little (trauma) or substantial (cholelithiasis) impact. Another concern is that trauma or cholelithiasis patients may have different socioeconomic backgrounds compared to meningioma patients, thus confounding the findings. However, socioeconomic factors were adjusted for in the Cox proportional hazards regression by taking insurance status into account. As in any study utilizing large population databases, concerns of miscoding in the database is an issue. However, miscoding is a random phenomenon distributed equally throughout the database. Therefore, assuming an equal proportion of miscoding among our three study populations, random miscoding would not have confounded this analysis. Finally, births that took place outside of California would have been missed by this analysis, possibly decreasing the strength of the calculated association between pregnancy and meningioma resection.

As with any populational study, elucidating a possible mechanism behind the observed correlation is not possible. Additional studies will therefore be required to investigate the specific behaviors of meningiomas during pregnancy in response to both hormonal and vasogenic changes.

Conclusion:

This study demonstrates a significantly higher rate of prior year pregnancy in patients admitted for meningioma resection compared to a trauma patient population (HR 1.86, 95% CI: 1.22-2.83). Patients admitted for meningioma resection have a lower rate of prior pregnancy compared to cholelithiasis patients. Patients with a known meningioma who are planning to become pregnant may be cautioned on their possible increased risk of requiring a resection postpartum.

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