Published in final edited form as:

Epilepsy Res. 2017 December ; 138: 116–123. doi:10.1016/j.epilepsyres.2017.10.012.

Contraception, Pregnancy, and Peripartum Experiences among Women with Epilepsy in Bhutan

Sheliza Halani, BASc^a, Lhab Tshering, BA^b, Esther Bui, MD, FRCPC^{a,c}, Sarah J. Clark, BSc^d, Sara J. Grundy, BA^d, Tandin Pem^c, Sonam Lhamo, MBBS^c, Ugyen Dema, MBBS^c, Damber K. Nirola, MBBS^c, Chenchu Dorji, MBBS^c, and Farrah J. Mateen, PhD, MD^{d,e} for the *Bhutan Epilepsy Project*

^aFaculty of Medicine, University of Toronto, 27 King's College Circle, Toronto, ON M5S 1A1, Canada

^bDepartment of Psychiatry, Jigme Dorji Wangchuck National Referral Hospital, Gongphel Lam, Thimphu, Bhutan

^cDepartment of Neurology, University Health Network, 399 Bathurst St., Toronto, ON M5T 2S8, Canada

^dNeurological Clinical Research Institute, Massachusetts General Hospital, 165 Cambridge St., Suite 600, Boston, USA, 02114

^eHarvard Medical School, A-111, 25 Shattuck St., Boston, USA 02114

1. Introduction

There are more than 25 million women with epilepsy (WWE) worldwide, approximately eighty percent of whom live in low- and middle-income countries (LMICs). (World Health Organization, 2017) In most LMICs, there are limited data on women's health in the context of epilepsy. Access to health services for both reproductive and neurological care may be limited. Few data are published on WWE in the context of contraception, pregnancy-related care, and labor and delivery in LMIC settings. This is striking since epilepsy often presents in childhood and typically affects women throughout their childbearing years.

Published reports highlight a range of issues involving WWE in LMICs. One study in Latin America found that only 10% of WWE received folic acid before pregnancy. (Kochen, 2011) This compares to the 48% of WWE who reported using folic acid when at risk of an unintended pregnancy in a separate study in high-income countries. (Herzog, 2017) Women in a study in South Korea decided to have fewer children because of their diagnosis of epilepsy. (Lee, 2013) Many had exaggerated perceptions of risk including: offspring

Send correspondence to: Farrah J. Mateen, MD, PhD, Department of Neurology, Massachusetts General Hospital, 165 Cambridge Street, #627, Boston, MA 02114, Ph. (617) 724 8653, fmateen@partners.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest: None declared.

developing epilepsy, offspring having a congenital anomaly if the mother had epilepsy, and other negative effects of seizures on the fetus.(Lee, 2013) In India, epilepsy in women is often hidden from male spouses due to stigma.(Thomas, 2011)

Obstetrical concerns in pregnant WWE may include increased risks of Caesarean section, pregnancy-induced hypertension, pre-eclampsia, peri-partum bleeding, and/or premature delivery.(Gedzelman, 2012) Risks for the fetus include small-for-gestational age (SGA) or risk of spontaneous abortion and/or perinatal death.(Gedzelman, 2012) There is an increased risk of major congenital malformations (MCMs) in children born to WWE compared to the general population, with 4.5% of children experiencing MCMs for women on monotherapy and 8.6% for women on polytherapy.(Gedzelman, 2012, Patel, 2016) Meanwhile, surveys in 5 Caribbean countries indicated that the majority of physicians were unaware that sodium valproate may cause MCMs.(Krauss, 2015) Since health systems in LMICs often have limited antiepileptic drug (AED) options, physicians also often have fewer options for optimally meeting the specific needs of WWE.

In the Kingdom of Bhutan, the prevalence of epilepsy is estimated to be approximately 1 in 130 people with an annual incidence of 50 per 100,000 people per year.(Duncan, 2007) Bhutan is typical of many LMICs since it has no practicing neurologist.(Ministry of Health, Bhutan, 2016) The various effects of epilepsy on women's health in Bhutan have yet to be specifically studied. However, Bhutan may be a country of particular interest from a health systems perspective, given the universal access to health services to Bhutanese citizens, with no out-of-pocket costs for medications or medical visits. The Bhutanese context may also provide insight into the scope of services that WWE can access in LMICs, but, for a variety of reasons, not engage.

Here, as part of the Bhutan Epilepsy Project, a prospective cohort study of people living with epilepsy, we interviewed WWE on their potential needs and perceived experiences. We focus on contraceptive practices and family planning, pregnancy history and outcomes, and peripartum experiences including breastfeeding as reported by women in the context of their epilepsy histories.

2. Materials and Methods

2.1 Ethics

The Research Ethics Board of Health of Bhutan, Institutional Review Board of Massachusetts General Hospital (USA) and Research Ethics Board of the University of Ottawa (Canada) approved this study. In cases of low literacy, a fingerprint of the participant was used instead of a signature.

2.2 Setting

The study was conducted in the Kingdom of Bhutan (population: 797,765).(World Bank, 2016) Bhutan is a lower middle income country with a gross national income per capita of 2,510 USD.(World Bank, 2016) In 2014, the total expenditure on health per capita was 60 USD.(World Bank, 2017) The life expectancy at birth is 69.8 years.(The World Bank, 2016) and the fertility rate (number of births per 1,000 women aged 15–49 years old in one year)

was 66.4 in 2012.(National Statistics Bureau, Bhutan, 2013) The child survival rate is 94% and is lower in rural areas (93%) compared to urban areas (97%).

In Bhutan, the healthcare workforce includes 251 physicians and 1070 nurses in 2016. (Ministry of Health, Bhutan, 2016) There are 31 hospitals among 20 geopolitical districts. Only one of these districts does not have a hospital. There are also basic health units and outreach clinics.(Ministry of Health, Bhutan, 2016) The healthcare system is decentralized with funding provided by the Royal Government of Bhutan for basic services, all health visits, and medications including AEDs. More specialized medical services that are not offered in Bhutan may be received in India, with the expenses paid by the Royal Government of Bhutan.(Ministry of Health, Bhutan, 2017)

In regards to perinatal care, the number of births attended by skilled health personnel in Bhutan increased from 64.5% in 2010 to 74.6% in 2015.(Annual Health Bulletin, 2016) Every district hospital has fetal ultrasound equipment, but sonography skill levels vary among health care professionals.(personal communication, May 6, 2017)

2.3 Recruitment and enrollment

WWE were recruited at the Jigme Dorji Wangchuck National Referral Hospital (JDWNRH) in person around the time of their medical visits, or later, by phone call. Participants were identified through an existing hospital registry of epilepsy patients at JDWNRH and were enrolled in the larger cohort study including neuroimaging, electroencephalogram (EEG), and often serum neurocysticercosis testing to help confirm the diagnosis and elucidate the potential etiologies of epilepsy.(Brizzi, 2016B, McKenzie, 2016, Bruno, 2017) Data on age, education, employment, seizure characteristics, and AEDs are derived from the initial enrollment evaluation we performed between 2014 and 2016.

Women were asked to retrospectively provide their fertility and pregnancy histories. Corroboration with the women's medical records was performed whenever available. Surveys occurred in person or by phone in 2016 and 2017, following participation in the other phases of the study. All study interviews were performed in the language of the participants, either Dzongkha or English.

Women were eligible for inclusion if they were currently between the ages of 20 and 59 years old, had a diagnosis of epilepsy defined as a lifetime history of 2 or more unprovoked seizures, and were available by telephone or in person during the study timeframe.

2.4 Survey Instrument

We referred to the literature for other published reports on pregnancy, contraception and perinatal care in WWE, focused on LMICs.(Sawhney, 1996, Thomas, 2001, Thomas, 2009, Kochen, 2011, Thomas 2011, Tomson, 2011) Based on these reports, we developed our own 10-category survey (Appendix 1). This survey was piloted in Bhutan, and, in collaboration with Bhutanese physicians (DKN, UD, CD) and interviewers (SL, TP, LT), we refined the questions to suit the local context in terms of vocabulary, relevance, and clarity. Each woman completed a structured survey on their experiences with contraception and pregnancy, as applicable. From prior surveys of these same participants, we had access to demographic

information, seizure frequency, AED use, education, and employment.(McKenzie, 2016, Saadi, 2016) The final survey instrument developed and used can also be found online for free public use at: goo.gl/k7H2PC.

2.5 Data analysis

Data were analyzed using basic descriptive statistics, including mean and standard deviation or median and interquartile range. Counts were given as the proportion of patients in the sample with a particular attribute. Subgroups of interest included ever pregnant versus not, rural versus urban (defined as inside or outside of the capital city Thimphu), limited education versus having a formal education (primary school and above), and unemployed versus employed (at the time of initial evaluation between 2014 and 2016).

The socioeconomic and epilepsy data were linked with the contraception, pregnancy, and peripartum data gathered. Factors such as family planning and contraception were reported for the entire cohort, whereas the pregnancy-related outcomes were compared for women for whom epilepsy affected at least one of their pregnancies versus those for whom epilepsy onset followed all of their pregnancies to date. For the women who had more than one pregnancy, the average inter-pregnancy interval was calculated by subtracting the age between all pregnancies for all multiparous women and subsequently, averaging these differences.

Comparisons were made using Fisher's exact test or a paired *t*-test with a pre-determined level of significance of $p<0.05$.

2.6 Comparative analysis

A search was completed to compare and contrast our findings among WWE with other LMICs (Table 4). The inclusion criteria for these papers were that they: reported on countries classified as LMICs by the World Bank at the time of the published study and specified AEDs as well as fetal and maternal outcomes. The search was performed in PubMed in July 2017 including English-language abstracts and/or full-length manuscripts of original research for the search years 1980–2017 We excluded articles that focused primarily on eclampsia-related seizures.

3. Results

3.1 Recruitment

There were 134 eligible WWE. Of 94 women who could be reached, 93 agreed to participate: 7 were interviewed in person due to convenience following a medical appointment, and 86 were recruited by phone. There was one refusal to participate (response rate 99%). We were unable to reach 40 potential women by phone due to their mobile phone being turned off or no response to our phone calls on three separate attempts at communication during the study enrollment period. Of all WWE in the cohort of eligible age, we were able to reach 69% (93 of 134).

3.2 Demographic and clinical characteristics of the study population

Among the 93 WWE, at the time of initial evaluation (median age 27 years, interquartile range 10 years, range 20–52 years), the modal decade of life was 20–29 years with 55 (59%) women in this category. The median age for the diagnosis of epilepsy was 20 years for the complete cohort (data not available for 4 WWE) and the average age of epilepsy onset was 18.4 years. Fifty women (54%) reported a prior pregnancy. For the ever-pregnant cohort, the median age for the diagnosis of epilepsy was 25 years (data not available for 2 WWE) and the average age at epilepsy onset was 21.4 years.

The most common self-reported seizure characteristics of the participants was “loss of consciousness” (87%) followed by “falling with stiffening and shaking” (62%). The average number of reported seizures per month was 3.8. At the time of enrollment, 24 women (26%) had not completed a primary school level of education, and 40 were unemployed (43%) (Table 1).

3.3 Contraception and family planning

Among the 56 women that responded on contraceptive practices, 50 were women with prior pregnancies and 6 were women without prior pregnancies. One woman did not provide the form of contraception used. Twenty-six women had never used contraceptives (47%), 21 women had used one contraceptive method (38%), 6 had used two methods (11%), and 2 had used three or more methods (4%). The most common contraceptive used was male condoms (14/29, 48% of women who had ever used contraception), followed by depot medroxyprogesterone acetate (DMPA) injections (13/29, 45% of women who had ever used contraception), intrauterine devices (5/29, 17%), progestin-only pills (POP) (4/29, 14%), combined oral contraceptive pills (OCP), (2/29, 7%), and other (2/29, 7%). There was no reported use of a diaphragm, emergency i-pill, or abstinence.

Forty-nine WWE responded to the question on family planning and education (including 46 with prior pregnancies). A majority received information on family planning and education (n=31, 63%): 21 had never used contraception including 10 who received information on family planning. Of the 27 that had used contraception, 20 received information on family planning. One additional participant did not respond on the contraception question.

3.4 Prenatal folic acid supplementation

Thirty-seven of 46 WWE (80%) women took folic acid supplementation during their pregnancies (data missing on 3 women). Data were available on the initiation of timing of supplementation for 35 of the women. Six of the 35 (17%) began supplementation in the first trimester, and the remaining 29 (83%) began supplementation in the second trimester.

Differences in folic acid supplementation as it relates to formal education were calculated for the subgroup of WWE and prior pregnancies. Within the group without formal education, 11 of 17 (65%) supplemented with folic acid, compared to 26 of 29 (90%) who completed at least primary school (4 WWE with prior pregnancies and at least a primary school education did not answer this question and were excluded) ($p=0.040$).

3.5 Pregnancy history and lactation

The peripartum characteristics of the ever-pregnant cohort are outlined in Table 2. The table is divided to separate the outcomes for the WWE with prior pregnancies in whom seizure onset occurred before or during the last pregnancy (i.e. epilepsy was present during at least one pregnancy) and the WWE whose pregnancies occurred prior to first seizure onset.

There were 38 WWE with seizures affecting at least one of their pregnancies. In this subgroup, the median age of onset of seizures was 16.5 years (interquartile range 11.8 years). The average maternal age at first pregnancy was 21.8 years (range: 15–34 years). The average number of pregnancies per woman was 2.3 (range: 1–8) and the average number of living children per woman was 2.1 children. There were a total of 86 pregnancies and 27 women were multiparous. Among the 24 of these 27 multiparous women for whom we know the ages at all pregnancies, the average inter-pregnancy interval for the cohort was 3.5 years. Thirty-six women attended prenatal visits and ultrasounds (95%). There were 8 WWE who had miscarriages and a total of 10 miscarriages in the cohort – 2 of them had 2 miscarriages each (data missing from 1 woman). There were 8 WWE who had Caesarean sections, 3 WWE who had twins, and 7 recognized cases of pre-term delivery among 5 women (<37 weeks gestational age). Thirty-seven (97%) responded affirmatively to breastfeeding during their pregnancies.

Of the 12 WWE whose onset of seizures followed their pregnancies, the median age of onset of seizures was 34.5 years (interquartile range=3.8 years). The average maternal age at first pregnancy was 20.4 years (range: 16–28 years). The average number of pregnancies per woman was 3.1 pregnancies (range: 2–6) and the average number of living children per woman was 2.8. There were a total of 37 pregnancies and an average inter-pregnancy interval of 3.8 years (for 11 of the 12 multiparous women). Data were not available for maternal ages of all pregnancies for one of the women. Eighty-three percent of this group (10/12) attended prenatal visits and ultrasounds. Four of the women had miscarriages and one of these women had 2 miscarriages. None of the women in this group had twins, Caesarean sections, or pre-term births. Eleven of 12 (92%) responded affirmatively to breastfeeding during their pregnancies. MCMs reported and were not well-recognized among participants.

Overall, 17 of the 38 women who had epilepsy during pregnancy had seizures during pregnancy, including two WWE who were not taking AEDs. Within the group of women who continued to take AEDs, most (63%, 15 of 24) had recognized seizures during pregnancy.

3.6 Post-hoc analysis of socioeconomic factors and pre-natal care

There are several reasons for which women did not have formal employment, including frequent seizures leading to self-perceived stigma (Brizzi, 2016A), pregnancy, caring for small children, working as a housewife, and not having formal education to obtain employment. Table 3 illustrates the attendance of pre-natal visits and fetal ultrasounds stratified by employment and educational attainment level in WWE, irrespective of the chronology of pregnancy and epilepsy. Fourteen of the 17 women (82%) in the limited

education group attended pre-natal fetal ultrasounds and clinic visits, while the percentages of women with some education who attended these visits were higher. Twenty of 21 (95%) of those who were employed at the time of the interview attended pre-natal visits and ultrasounds for their prior pregnancies, however this did not differ significantly from those without formal employment ($p=0.20$).

3.7 Antiepileptic drug use

At the time of enrollment into the cohort, 55% took AED monotherapy ($n=51$), 37% were on polytherapy ($n=34$), and 9% ($n=8$) were not on an AED (Table 1). The most frequently used monotherapy was phenytoin ($n=19$). The most frequently used polytherapy was either the combination of phenobarbital and carbamazepine (4 patients) or the combination of phenytoin and sodium valproate (4 patients).

4. Discussion

We analyzed the contraceptive, pregnancy, and peripartum histories of community-dwelling WWE in the lower middle-income country of Bhutan. Our study provides insights into the experiences of WWE in a resource limited setting including a remote and rural population. We report on a clinically well-characterized cohort of epilepsy participants with confirmed diagnoses by subspecialized neurologists. Our results focus on the female experience of having epilepsy in the reproductive age range and the medical treatment of WWE in the universal health system of Bhutan. Although this work was limited by the retrospective nature of our data collection, it provides new insights into the life histories of WWE that would otherwise take several years to decades to acquire prospectively. Long windows for data collection are less adept for setting policy in the short term for small populations, especially when specific interventions could be readily implemented. Given the at times sensitive nature of women's reproductive issues, the self-reported aspect of our survey provides insights into the experiences of WWE in ways that traditional registries and official reporting may not be designed to disaggregate or flexible and sensitive enough to capture.

Our most actionable finding relates to folic acid supplementation for WWE in resource limited settings. Although folic acid supplementation was used by 80% of WWE, the majority commenced supplementation during the second trimester of pregnancy. Given the higher risk of WWE to experience teratogenicity (Tomson, 2011, Vashisth, 2013, Zhang, 2011, Thomas, 2011), the preconception use of folic acid and increased dose for WWE on folate antagonist AEDs such as valproic acid, should be emphasized. Since folic acid is inexpensive, on the World Health Organization's Essential Medicines List, and available in Bhutan, the knowledge to start folic acid in all WWE of childbearing potential should be formalized into guidelines and policy. Indeed, 95% of all WWE in this study reported attending pre-natal visits.

In India, preconception evaluation, folic acid prescriptions, detailed screening for fetal malformations by serum alpha protein and ultrasonography between 14 to 18 weeks have been formalized into programs for WWE.(Begum, 2013) Such an approach may be borrowed in Bhutan but focus on a "train the trainer" approach at the community health care worker level, since folic acid supplementation requires no prescription or monitoring.

Although we found a statistically significant association between higher education level and folic acid supplementation in *post hoc* analyses, we were unable to control for potential confounding conditions such as rural location given our small sample size. Our cutoff for educational attainment was also very low, at just primary school completion. The influence of rural location of the WWE remains important for future studies.

Some WWE are at risk of potential interactions between oral contraceptive medications and their AEDs, however the extent to which this is an important issue for WWE in LMICs has been under-reported. Among 29 Bhutanese WWE reporting lifetime contraceptive use, 18 used DMPA or an intrauterine device for contraception at one point in their lives, which are not likely influenced by enzyme-inducing AEDs. However 6 women used either a progestin-only or combined oral contraceptive pill, both of which are influenced by enzyme-inducing AEDs. Of these 6 WWE, 5 of them took at least one AED (e.g. phenobarbital, carbamazepine) in which these interactions were relevant. Since oral hormonal contraception combined with enzyme-inducing AEDs has a significantly greater failure rate than hormonal contraceptives combined with no AED (Thomas, 2015), these drug-drug interactions remain relevant to WWE in LMICs especially. Without making specific recommendations on contraception, it is important to recognize and counsel WWE that some AEDs are unlikely to influence contraceptive steroids, such as gabapentin, pregabalin, and gabapentin. (Thomas, 2015) Moreover, IUDs and DMPA may avoid these drug-drug interactions altogether. (Lee, 2013; Espinera, 2016) In the Epilepsy Birth Control Registry, a web-based survey in the U.S. of more than 1000 WWE, the use of IUDs among WWE was higher than in the general population (17.4% vs. 6.3%), likely due to the lack of drug-drug interactions with IUDs. (Herzog, 2016)

In their lifetimes, 37% of WWE in Bhutan reported unmet family planning needs. This is higher than in the general Bhutanese population in 2015, reporting that same number at 11.7%. (Ministry of Health of Bhutan, 2016) Since our study did not engage a control group, we are unable to comment on whether there is a true difference; however, it seems likely that WWE have at least the same if not higher unmet family planning needs than the average population in the same location.

Prenatal visits and fetal ultrasound use were high among WWE (95%) and rival the coverage found in high income countries (98%) and exceed the coverage reported from other LMICs (approximately 68%). (Toan 2012) WWE fared similarly to the average Bhutanese population in this regard with 94% of urban and 84% of rural Bhutanese women receiving prenatal care in 2012. (National Statistics Bureau of Bhutan, 2013) Attendance at prenatal visits however does not equate to optimal delivery services or peripartum epilepsy care: only 4 facilities in Bhutan had comprehensive emergency obstetric services in the most recently available reporting year (2000). (Liabsuetrakul, 2007) Among WWE taking AEDs during pregnancy in Bhutan, nearly two-thirds (63%) continued to experience seizures. We did not explore reasons for seizures during pregnancy but prior research in this cohort found sub-therapeutic AED dosing to be a leading contender. (McKenzie, 2015) By contrast, in India, 25% and 53% of WWE experienced peripartum seizures in two separate studies. (Sawhney, 1996; Thomas, 2009)

Among WWE in whom epilepsy affected at least one pregnancy, the average number of living children per woman was 2.1, and the average number of pregnancies was 2.3. This is similar to the total fertility rate of 2.3 children per Bhutanese woman reported in 2015. (Ministry of Health of Bhutan, 2016) WWE however reported a high miscarriage rate: 22% of WWE with concurrent epilepsy and pregnancies reported at least one miscarriage. Since miscarriages are often under-reported and early, especially first trimester, miscarriages may be under-recognized, this number is high. In WWE overall, there is a 1.2 to 3-fold increase in risk of stillbirths and neonatal deaths and higher rates of Caesarean sections. (Thomas, 2009) In our study, the gestational age of the reported miscarriages was not obtained; therefore, we are unable to differentiate whether the reported numbers include spontaneous abortions (before the period of fetal viability) or stillbirths or both. The Caesarean section rate in Bhutanese WWE was relatively high among those with epilepsy prior to pregnancy. A comparative literature search, as seen in Table 4, shows that spontaneous abortions were 8.5% and perinatal death was 2.3% of all births among WWE in Latin America. (Kochen, 2011) In Kerala, the spontaneous abortion rate of 4.5% and the stillbirth/intrauterine death rate was 1.5%. (Thomas, 2009) Given the few studies that report the inter-birth interval among WWE, the finding of 3.5 years for Bhutanese WWE deserves future international comparative data.

Nearly all WWE in Bhutan reported breastfeeding, in keeping with World Health Organization recommendations for postpartum women in general. Infant monitoring when mothers are breastfeeding is advisable when WWE are taking phenobarbital or newer AEDs due to these drugs' slow rate of elimination in nursing infants. (Bar-Oz, 2000) Infant monitoring includes checking for jaundice and drowsiness, monitoring psychomotor development, and assuring adequate infant weight gain. In some cases, it also includes checking the infant's plasma drug levels. (Davanzo, 2013) Bhutanese WWE were most often taking phenytoin which has a low degree of penetration into breast milk, and carbamazepine which has a moderate milk-to-plasma ratio. (Veiby, 2015) AED levels are presently not available for measurement through laboratories in Bhutan. By comparison, in nearby Western China, only 17% of infants of WWE received pure breastfeeding, 25% received mixed feeding, and 58% received exclusively artificial formula feeding. (He, 2017) The authors hypothesized that the low rate of breastfeeding was related to insufficient social advocacy and health education. For example, some Chinese WWE believed that AED use would affect the health of their child negatively via the breast milk, although breastfeeding of WWE is safe. (He, 2017) Although our survey did not inquire whether WWE exclusively breastfed, in Bhutan we speculate that this is most often because of the lack of availability of formula and related alternative options.

Our study is subject to several specific limitations. Some topics were difficult to obtain information on such as marital status and whether pregnancies or contraception were wanted or unwanted. It is possible, even likely, that specific details were unreported due to taboos in Bhutanese society. As one example, only 6 WWE without prior pregnancies responded to the question on contraception and 5 out of 6 responded negatively. Another example regards therapeutic abortion. In Bhutan, the termination of pregnancy is illegal except to save the woman's life, and only one abortion was officially noted in 2015. (Bhutan Abortion Law, Ministry of Health of Bhutan, 2016) However, therapeutic abortions are performed for out of

pocket payments in neighboring India and may go uncounted. Unplanned pregnancy has been studied in rural Bhutan: respondents reported a 1% prevalence of abortion but 57% of respondents could name someone else who had undergone one.(Choden, 2015) In order to mitigate stigma during our interviews, we employed female interviewers to conduct the reproductive health survey and made our survey clearly distinct from any official government surveys. The impact of this strategy is however unclear.

Since our data gathering depended on WWE's self-report and retrospection on their pregnancies, it is in general prone to recall bias and response bias as well as potential educational and language barriers. In some cases there were non-responses and missing data. Since we focused on WWE and asked about pregnancies retrospectively, some WWE had their first recognized seizure *after* their last pregnancy. This occurred in 12 cases, and led to separation of our data into smaller subgroups. Given the small sample sizes overall, more sophisticated analyses and prediction models could not be performed. In some cases, eclampsia and pseudo-seizures may have occurred; however, we believe these conditions were generally rare in this population given the careful clinical evaluation and diagnostic evaluation of each case. Finally, many Bhutanese WWE were - and continue to be - nomadic; their distance to the health center was not constant over their lifetimes and their remoteness likely fluctuated with season and time as urbanization continues.

By contrast, the strengths of our study include the well-depicted group of WWE and prior pregnancies in a LMIC. While partially comparative data derive India and Latin America, we provide new information from Southeast Asia for global comparisons. Our study also includes the educational and employment statuses of WWE for contextualization. A recent systematic review found important variation exists in maternal and fetal outcomes among WWE by geographical region, economic status, and time.(Allotey, 2017) As such, our survey instrument may be useful for other future studies in LMICs as a concise tool to understand reproductive and maternal histories among WWE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported in part by the Charles Hood Foundation.

References

- Allotey J, Aroyo-Manzano D, Lopez P, et al. Global variation in pregnancy complications in women with epilepsy: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* 2017; 215:12–19. [PubMed: 28591672]
- Bar-Oz B, Nulman I, Koren G, et al. Anticonvulsants and breast feeding: a critical review. *Paediatr Drugs.* 2000; 2(2):113–26. [PubMed: 10937463]
- Begum S, Thomas SV. Women with epilepsy in reproductive age group: special issues and management strategies. *J Assoc Physicians India.* 2013; 61(8 Suppl):48–51. [PubMed: 24818330]
- Brizzi K, Deki S, Tshering L, et al. Knowledge, attitudes and practices regarding epilepsy in the Kingdom of Bhutan. *Int Health.* 2016A; 8(4):286–91. [PubMed: 27160683]

- Brizzi K, Pelden S, Tshokey T, et al. Neurocysticercosis in Bhutan: a cross-sectional study in people with epilepsy. *Trans R Soc Trop Med Hyg.* 2016B; 110(9):517–526. [PubMed: 27794094]
- Bruno V, Klein J, Nidup D, et al. Yield of Brain MRI in Clinically Diagnosed Epilepsy in the Kingdom of Bhutan: A Prospective Study. *Ann Glob Health.* 2017; 2017 Epub ahead of print, doi: <http://dx.doi.org/10.1016/j.aogh.2017.02.001>.
- Choden J, Pem R, Pathak A. Prevalence, determinants, and outcomes of unplanned pregnancy and perspectives on termination of pregnancy among women in Nganglam, Bhutan. *Bhutan Health Journal.* 2015; 1(1)
- Davanzo R, Dal BS, Bua J, et al. Antiepileptic drugs and breastfeeding. *Ital J Pediatr.* 2013; 39(50)doi: 10.1186/1824-7288-39-50
- Duncan J. Neurology in Bhutan. *Neurology Asia.* 2007; 12:57.
- Gedzelman E, Meador KJ. Antiepileptic drugs in women with epilepsy during pregnancy. *Ther Adv Drug Saf.* 2012; 3(2):71–87. [PubMed: 25083227]
- Espinera AR, Gavvala J, Bellinski I, et al. Counseling by epileptologists affects contraceptive choices of women with epilepsy. *Epilepsy & Behavior.* 2016; 65:1–6. [PubMed: 27829186]
- He S, Zhu H, Qiu X, et al. Pregnancy outcome in women with epilepsy in Western China: A prospective hospital based study. *Epilepsy & Behavior.* 2017; 74:10–14. [PubMed: 28666184]
- Health Management & Information System, Policy & Planning Division, Ministry of Health, Royal Government of Bhutan, Thimphu. Annual Health Bulletin 2016. 2016. <http://www.health.gov.bt/wp-content/uploads/ftp/annual-health-bulletins/Annual%20Health%20Bulletin-2016.pdf> Accessed on June 18, 2017
- Herzog AG, MacEachern DB, Mandle HB, et al. Folic acid use by women with epilepsy: Findings of the Epilepsy Birth Control Registry. *Epilepsy Behav.* 2017; 72:156–160. [PubMed: 28605689]
- Herzog AG, Mandle HB, Cahill KE, et al. Contraceptive practices of women with epilepsy: Findings of the epilepsy birth control registry. *Epilepsia.* 2016; 57(4):630–637. [PubMed: 26880331]
- Human Resource Division, Ministry of Health, Bhutan. Human resources for health country profile Bhutan. <http://www.health.gov.bt> Last accessed on August 15, 2017
- Jain S, Maheshwari MC. A prolonged prospective follow-up study of 306 epileptic patients in New Delhi. *Acta Neurol Scand.* 1991; 84:471–474. [PubMed: 1792851]
- Kochen S, Salera C, Seni J. Pregnant women with epilepsy in a developing country. *Open Neurol J.* 2011; 5:63–7. [PubMed: 22046203]
- Krauss G, Sandy S, Corbin DO, et al. Epilepsy Care in Southern Caribbean. *Epilepsy and Behav.* 2015; 51:267–272.
- Lee SM, Nam HW, Kim EN, et al. Pregnancy-related knowledge, risk perception, and reproductive decision making of women with epilepsy in Korea. *Seizure.* 2013; 22(10):834–839. [PubMed: 23890718]
- Liabsuetrakul T, Peeyananjarassri K, Tasee S, et al. Emergency obstetric care in the southernmost provinces of Thailand. *Int J Qual Health Care.* 2007; 19(4):250–256. [PubMed: 17575277]
- McKenzie ED, Nirola DK, Deki S, et al. Medication prescription and patient-reported outcome measures in people with epilepsy in Bhutan. *Epilepsy Behav.* 2016; 59:122–127. [PubMed: 27131914]
- National Statistics Bureau, Bhutan and Asian Development Bank. Bhutan Living Standards Survey 2012 Report. 2013. <https://www.adb.org/sites/default/files/publication/30221/bhutan-living-standards-survey-2012.pdf> Last accessed on June 18, 2017
- Patel SI, Pennell PB. Management of epilepsy during pregnancy: an update. *Ther Adv Neurol Disord.* 2016; 9(2):118–129. [PubMed: 27006699]
- Saadi A, Patenaude B, Nirola DK, et al. Quality of life in epilepsy in Bhutan. *Seizure.* 2016; 39:44–48. [PubMed: 27257785]
- Sawhney H, Vasishta K, Suri V, et al. Pregnancy with epilepsy – a retrospective analysis. *Int J Gynaecol Obstet.* 1996; 54(1):17–22. [PubMed: 8842813]
- Thomas SV. Controversies in contraception for women with epilepsy. *Ann Indian Acad Neurol.* 2015; 18(3):278–283. [PubMed: 26425002]
- Thomas SV. Managing epilepsy in pregnancy. *Neurol India.* 2011; 59(1):59–65. [PubMed: 21339661]

- Thomas SV, Nair A. Confronting the stigma of epilepsy. *Ann Indian Acad Neurol*. 2011; 14(3):158–163. [PubMed: 22028525]
- Thomas SV, et al. Maternal and obstetric outcome of women with epilepsy. *Seizure*. 2009; 18(3):163–166. [PubMed: 18805707]
- Thomas SV, et al. Pregnancy in women with epilepsy: preliminary results of Kerala registry of epilepsy and pregnancy. *Neurol India*. 2001; 49(1):60–66. [PubMed: 11303244]
- Toan, TK. Doctoral thesis at the Nordic School of Public Health NHV Gothenburg, Sweden: 2012. Antenatal and Delivery Care Utilization in Urban and Rural Contexts in Vietnam: A study in two health and demographic surveillance sites.
- Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol*. 2011; 10(7):609–17. [PubMed: 21652013]
- Vashisth K, Singh R, Medhi B. Effect of in utero Exposure to Antiepileptic Drugs on Cognitive Function in Children. *Pharmacology*. 2013; 92:315–318. [PubMed: 24335199]
- Veiby G, Bjørk M, Engelsen BA, et al. Epilepsy and recommendations for breastfeeding. *Seizure*. 2015; 28:57–65. [PubMed: 25837494]
- The World Bank. Bhutan. The World Bank. 2016. <http://data.worldbank.org/country/bhutan> Accessed on July 29, 2017
- World Health Organization. Epilepsy. World Health Organization. 2017. www.who.int/mediacentre/factsheets/fs999/en/ Accessed on July 29, 2017
- Zhang LL, Zeng LN, Li YP. Side effects of Phenobarbital in epilepsy: a systematic review. *Epileptic Disord*. 2011; 13(4):349–365. [PubMed: 21926048]

Highlights

- Few reports exist on reproductive health and epilepsy in developing countries.
- We surveyed 93 women with epilepsy [125 pregnancies] in the Kingdom of Bhutan.
- Nearly half of women with epilepsy had never used contraception.
- Folic acid use in pregnancy was associated with education and often began late.
- Lactation postpartum was practiced nearly universally.

Table 1

Demographic and Clinical Characteristics of WWE in the Study Population, n = 93

Current Age Category, n (%)	
20–29y	55 (59)
30–39y	25 (27)
>=40y	13 (14)
Education Completed, n (%)	
None	24 (26)
Primary School	21 (23)
Secondary School	15 (16)
High School	18 (19)
College	15 (16)
Employment, n (%)	
Unemployed	40 (43)
Farmer	15 (16)
Student	7 (8)
Business/Technology	18 (19)
Government	6 (6)
Education	5 (5)
Healthcare	2 (2)
Income, n (%)	
Family Bank Account	88 (95)
Seizure characteristics, n (%) ¹	
Loss of consciousness	81 (87)
Falling with stiffening and shaking	58 (62)
Falling no shaking	11 (12)
One body part shaking	10 (11)
Staring spells	11 (12)
Unusual behavior	27 (29)
Sensory events	30 (32)
Unknown/other	30 (32)
Current AED Use, n (%)	
0 AED	8 (9)
1 AED	51 (55)
2 AED	26 (28)
3 AED	8 (9)
Phenytoin	34 (37)
Carbamazepine	30 (32)
Phenobarbital	21 (23)
Levetiracetam	15 (16)

¹Note that WWE may have more than one of the seizure characteristics listed in Table 1.

Sodium valproate	17 (18)
Benzodiazepines	10 (11)
Lamotrigine	2 (2)
Gabapentin	1 (1)

AED = anti-epileptic drug

Table 2

Pregnancy-related outcomes among WVE, n=50

Pregnancy Outcomes	Contemporaneous Epilepsy and Pregnancy			Epilepsy Succeeding Pregnancy		
	Number of Respondents (n)	Number Affirmative (n)	%	Number of Respondents (n)	Number Affirmative (n)	%
Prenatal visits/ultrasounds	38	36	95	12	10	83
Miscarriages	37	8 ²	22	12	4 ³	33
Pre-term delivery ⁴	36	5	14	11	0	0
Caesarean section	38	8	21	12	0	0
Twins	38	3	8	12	0	0
Breastfeeding	38	37	97	12	11	92

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

²Two of these women had 2 miscarriages each.

³One of these women had 2 miscarriages.

⁴There were 7 pre-term deliveries among 5 women. Two of the women had 2 pre-term deliveries each.

Table 3

Highest Educational Attainment and Present Employment Status compared with Prenatal Visits/Fetal Ultrasounds in WWE reporting Prior Pregnancies, n=50

	Pre-Natal Visits/Ultrasounds	
	n, (%)	
Highest educational attainment		
None	3 (18)	14 (82)
Primary School	0 (0)	11 (100)
Secondary School	1 (11)	8 (89)
High School	0 (0)	12 (100)
College	0 (0)	1 (100)
Presently employed		
No	3 (10)	26 (90)
Yes	1 (5)	20 (95)

Table 4

Highest Educational Attainment and Present Employment Status by Lifetime Contraceptive Use in WWE,
n=55

	Lifetime Contraceptive Use n (%)	
Highest educational attainment		
None	8 (44)	10 (56)
Primary School	8 (44)	10 (56)
Secondary School	2 (50)	2 (50)
High School	5 (45)	6 (54)
College	3 (75)	1 (25)
Presently employed		
No	12 (50)	12 (50)
Yes	14 (45)	17 (55)
Urbanicity		
Thimphu District	5 (38)	8 (62)
Outside of Thimphu District	21 (50)	21 (50)