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Summary

Pregnancy registries are essential sources to gain medical and therapeutic knowledge in women with epilepsy who are pregnant or have the desire to give birth. The benefit of treatment for the mother has to be balanced with the prenatal and postnatal risk for the child. To gain reasonable medical evidence, pregnancy registries have to include an adequate and representative number of pregnant women with epilepsy. They will have to observe women during pregnancy and delivery, as well as the foetus respectively the child during its development. In addition, different health care providers have to coordinate their efforts, sharing data while preserving the mother privacy interests. Given these requirements, the multitude of antiepileptic drugs, and the poor knowledge concerning the important implications of the adopted therapy by potential mothers with epilepsy, the rate of patient inclusion in pregnancy registries is still insufficient to provide reliable recommendations for an appropriate medical management. An ethical approach as outlined here aims to overcome some of these obstacles.

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Keywords: Pregnancy, epilepsy, antiepileptic drugs, pregnancy registries, ethics

Considérations éthiques en lien avec l'inclusion de femmes épileptiques dans des registres de grossesse

Les registres de grossesse sont des sources essentielles de connaissances médicales et thérapeutiques chez les femmes épileptiques enceintes ou désirant donner naissance. Le bénéfice du traitement pour la mère doit être mis en balance avec le risque pré- et postnatal pour l'enfant. Pour obtenir une preuve médicale raisonnable, les registres de grossesse doivent inclure un nombre adapté et représentatif de femmes enceintes souffrant d'épilepsie. Ces femmes devront être suivies pendant leur grossesse et leur accouchement, et le fœtus, puis l'enfant, dans son développement. De plus, différents prestataires de soins de santé devront

coordonner leurs efforts et partager des données tout en préservant la vie privée de la mère. Face à de telles exigences, à la grande variété de médicaments antiépileptiques et au manque de connaissances sur ce qu'implique le traitement adopté par les mères potentielles souffrant d'épilepsie, le taux de patientes incluses dans les registres est encore insuffisant pour fournir des recommandations fiables pour une prise en charge médicale adaptée. Une approche éthique, telle qu'exposée ici, vise à surmonter certains de ces obstacles.

Mots clés : Grossesse, épilepsie, médicaments antiépileptiques, registres de grossesse, éthique

Ethische Überlegungen zum Einschluss von Frauen mit Epilepsie in Schwangerschaftsregister

Schwangerschaftsregister sind unverzichtbare Quellen zum medizinischen und therapeutischen Wissen bei schwangeren Epilepsie-Patientinnen oder epilepsiekranken Frauen mit Kinderwunsch, wenn es darum geht, den Nutzen einer Behandlung für die Mutter gegen die prä- und postnatalen Risiken für das Kind abzuwägen. Für stichhaltige medizinische Evidenz bedarf es einer ausreichenden Zahl an Schwangeren mit Epilepsie in den Schwangerschaftsregistern. Erfasst werden müssen Daten zum Schwangerschaftsverlauf und zur Geburt bei diesen Frauen sowie zur Entwicklung des Fetus bzw. des Kindes. Ferner müssen unterschiedliche medizinische Leistungserbringer ihre Anstrengungen koordinieren und entsprechende Daten unter gleichzeitiger Wahrung der Datenschutzinteressen der Mutter zur Verfügung stellen. Angesichts dieser Anforderungen, der Vielzahl an Antiepileptika und des spärlichen Wissens um die bedeutenden Auswirkungen der jeweiligen Therapie auf potenzielle epilepsiekranken Mütter ist die Zahl der in Schwangerschaftsregister eingeschlossenen Patientinnen noch nicht ausreichend gross, um zuverlässige Empfehlungen bezüglich des angemessenen medizinischen Managements aussprechen zu können. Ein ethischer Ansatz in dem hier aufgezeigten Sinne dient dazu, einen Teil dieser Hindernisse zu überwinden.

Schlüsselwörter: Schwangerschaft, Epilepsie, Antiepi-

Introduction

Epilepsy and pregnancy could have a combined deleterious effect on one another: pregnancy can worsen the evolution of the epilepsy, and epilepsy and antiepileptic drugs (AED) can complicate the normal course of pregnancy and the in-utero foetal development with immediate or more long-term complications for the expected child. Pregnancy registries represent the most utilized research method to better understand and prevent possible harm to the mother and the foetus. The physical risks of participating in these clinical registries is considered minimal and the possibility to gain knowledge about the underlying disease and the safety of different AEDs is very important for the foetus and child, and for future pregnancies for all women sharing the same conditions. Yet, the inclusion of pregnant women in pregnancy registries as well as the necessary long-term follow-up is difficult to achieve, and as a result pregnancy registries may not provide the necessary results to advise and appropriately treat pregnant women with epilepsy. To improve this situation, it is important to understand the ethical issues governing the participation of pregnant women with epilepsy in pregnancy registries.

1. Pregnancy and epilepsy: in search of more medical evidence

Epilepsy is a disorder that might lead to a more complicated course of pregnancy. Pregnancy can lead to an increase in the number of seizures compared to the pre-pregnancy period, irrespective of any treatment modifications [1]. Seizures themselves can affect the foetus and the delivery [2]. About 3 to 5 births per 1000 are from women with epilepsy. Additionally there are women whose first seizure occurs during pregnancy without a prior diagnosis of epilepsy. There is thus a great need to train health care providers to appropriately care for these women during their pregnancy [3]. For the mother, the foetus and the child, epilepsy is indeed a major challenge to be addressed during pregnancy as well as during the neonatal and postnatal periods. In 2008, a first statement on health outcomes of AED use in pregnant women established guidelines to address the risk of teratogenicity and major congenital malformations as well as minor malformations and long-term cognitive disorders. At this time, a lack of medical evidence was already pointed out regarding the underlying mechanisms leading to pathology and the variant findings across different AEDs or combinations of AEDs [4]. A recent systematic review and meta-analysis confirmed that pregnant women with epilepsy, compared to pregnant women without epilepsy, have a

small but significantly higher risk of complications of spontaneous miscarriage, antepartum haemorrhage, post-partum haemorrhage, hypertensive disorders, preterm induction of labour, increased caesarean section, preterm birth and foetal growth restriction [5]. The authors show that most of these complications are found in women taking antiepileptic drugs. This review took into account observational studies published between 1990 and 2015, with old and new AEDs. Meador, commenting on this meta-analysis, has reiterated that knowledge about pregnancy outcomes and adverse outcomes in neonates and children exposed in utero to AEDs is still insufficient [4]. André et al. have also identified the need for more monitoring data as well as randomized controlled studies on newer AEDs [6].

The main limitation for gathering more medical evidence in order to better manage pregnant women with epilepsy lies in the difficulty to include pregnant women in clinical research.

2. Pregnant women and clinical research

Pregnant women are legally considered as “vulnerable persons” for interventional and pharmacologic research concerning AED. This classification was made not primarily because of the risk of the research for the women themselves, but due to the risk for the embryo respectively the foetus (after 9 weeks of pregnancy) and its future development in the neonatal and childhood periods. The interests of the mother and the foetus are obviously closely related, but they could also be in opposition when the necessary treatment of the mother might be harmful for the foetus. The whole situation becomes even more complex because regulatory organs, such as the FDA, EMEA or Swissmedic don't require interventional clinical research in pregnant women or children at the time of a new drug approval. They will ask for complementary monitoring after the drug is approved and marketed. The situation resembles an off-label prescription of AED in a pregnant woman with a moral legitimacy higher than pre-approval interventional research, which could have established the safety profile of the AED in the first place. Some researchers have tried to justify a more invasive approach by advocating that the foetus is a patient holding rights of a person. Their aim was to help the ethical review committee supporting a research that could benefit the foetus with limited infringement of the mother's autonomy [7]. In countries like Switzerland, this approach is difficult to follow, as the foetus is not legally considered a person. In the USA, the National Institute of Health (NIH) has proposed to encourage the development of clinical research in pregnant women and the acquisition of medical evidence for their treatment. The NIH recommendations included 3 major points: identifying specific areas in which clinical research is pressing, supporting ethical committees to accept more

widely research in pregnant women, and reclassifying pregnant women from “vulnerable patients” to a mere scientifically “complex population” [8]. In order to better understand the barriers to perinatal research and randomized controlled research in pregnant women, Brandon et al. have conducted a qualitative research with investigators and members of ethical committees in the field of mental health in pregnant mothers. They identified four issues that are equally relevant to epilepsy and pregnancy: i) the difficulty of identifying a control group with placebo or reference treatment; ii) the safety concerns for the mother at risk of under-treatment, for the foetus concerning congenital and teratogen risks, for the child concerning its cognitive development; iii) the demanding process of inclusion of participants and the conceptual difference between clinical care and clinical research; iv) the possible restriction of the autonomy of pregnant women due to their possible low level of comprehension, the consideration of the relationship between the father and the foetus/child, and the risk of breaches in confidentiality due to the involvement of numerous research stakeholders [9]. Randomised clinical research with pregnant women would be better accepted in the absence of off-label treatment. Yet, in epilepsy and pregnancy, the main research concerns just such off-label research looking for the effects of AEDs on mothers, fetuses and children. Acquiring strong medical evidence in pregnancy and epilepsy is for these reasons difficult, and until today medical research has relied upon observational studies and clinical registries. These pregnancy registries can moreover help facilitate the design of possible future randomised controlled studies.

3. Pregnancy registries

Pregnancy registries have been widely used to learn about pregnant women with epilepsy treated with AEDs. The UK Epilepsy and Pregnancy Register, for example, enabled the identification of the increased risk of major congenital malformations under a combination therapy or a therapy with valproate [10]. The Florida Medicaid registry showed that these types of results could be translated into practice, as the use of valproate decreased significantly favouring second-generation AEDs [11]. Nevertheless, registries have their limitations. Their target population is not always well defined and the findings may not be generalizable. Information on exposure to AED may be only partial or inaccurate, outcomes data can be incomplete as spontaneous abortions or stillbirths might not be reported. Other registries such as the National Swedish Medical Birth Registry, or the European registration of congenital abnormalities and twins (EUROCAT) may provide information that could help identify complications due to the in-utero exposure of AED, but these registries do not provide the basis to assure the best management

of pregnant women with epilepsy [12].

The Agency for Healthcare Research and Quality (AHRQ) published in their user guide for clinical registries a special chapter on pregnancy registries (pp. 135-169). This guide identifies the variables commonly collected and the issues to consider for interpreting the results of these registries [13]. Stating that pregnancy registries are different from other clinical registries, the guide requires that women be enrolled prospectively, a meaningful control group established, sufficient statistical power achieved, and that accurate data on drug exposure be collected. Additionally, to measure reproducible outcomes in pre- and postnatal periods, different sources of information from various health care providers are required.

The AHRQ's definition of pregnancy registries (“Pregnancy registries are prospective observational studies specifically designed to collect clinically relevant data and provide information for treating or counseling not only women who are pregnant but also women of childbearing potential”) concerns both pregnancy registries that collect data on epilepsy treatment, and pregnancy exposure registries required for the post-marketing safety studies of new AEDs. Post-marketing registries are not randomised and may harbour limitations when a pharmaceutical company, only interested in its own product, is funding them. Therefore it is important to identify the different types of pregnancy registries i.e. national registries, independent academic registries or pharmaceutical company registries, and to better understand their purpose, modes of enrolment, types of measured outcomes or possible control groups and duration of follow-up.

The epilepsy Therapy Development Project Work Group on Teratogenicity has reviewed pregnancy registries and methodological aspects [14]. To avoid bias and confounding factors, they recommend that all eligible women be included prospectively and that the included women should accept to provide all information necessary for profiling the risks of complicated pregnancy or foetal problems. Ideally, the participating women would contribute to the regular monitoring of AED exposure concerning the type of drug, dose, and blood levels. In addition, they would be asked to accept to be part of the post-partum follow-up questionnaire, including measurements of pre-defined possible outcomes for the neonate and the child.

These requirements may however be too demanding for women from the control group who will have to balance the burdens of the study with a possible contribution to a common good of research. Additionally, the findings of early malformations or late cognitive disorders will depend upon the length of child observation, the longer the observational period, the higher the possibility to identify these disorders. The assessment of these outcomes thus depends heavily on the rate of women and children lost to follow-up in the registry.

To sum up, the inclusion of epileptic women in preg-

nancy registries requires quite constraining demands from the participants in order for the registry to be scientifically valid. These conditions may dissuade the pregnant women to consent to participate in the pregnancy registry and finally make the registry futile. As a result, and in order to gain the necessary knowledge for the management of pregnant women with epilepsy, ethical issues have to be further explored about the decision process to create and run pregnancy registries in women with epilepsy.

4. Ethical considerations for developing pregnancy registries

The aim of clinical registries in pregnancy and epilepsy is not only to gain scientific knowledge and safety data on the use of AED, but also to provide counselling and support to epileptic women who are pregnant or are considering pregnancy. The previous section shows that creating and managing pregnancy registries is a complex process. The main issues concern the identification of the most appropriate population with epilepsy to be included in pregnancy registries, the information provided to the selected women, and the responsibility of the participating health care providers in the management and communication of the results from these registries.

In contrast to the potential heavy burden of participating in pregnancy registries, the direct benefits for the mothers included in the registry are relatively small. They can expect better information and follow-up care of their epilepsy during this and future pregnancies. The foetus being exposed to possible maternal seizure and AED will have no direct benefit, with the exception of a possible long-term follow up after birth, which could detect and possibly mitigate minor malformations and cognitive disorders. Yet, few studies have followed the children beyond 6 years, and it is still uncertain as to whether negative effects on IQ might be reversible [15]. Other pregnant women with the same kind of epilepsy as well as their foetus may benefit from the findings, if the clinical registries are scientifically valid and powered statistically, and if the pregnant mothers are exposed to the same type and dosage of AED. All these requirements for generalizable and useful clinical registries are still burdened with a high level of uncertainty in terms of measured outcomes and scientific validity. This makes it difficult to include and keep women in the registry.

French et al. have reviewed the ethical issues governing participation in clinical registries and dissemination of their findings [16]. As pregnancy registries aim to generalize knowledge, their design and conduct depends upon the legal requirements of research on human subjects, and informed consent from participants is necessary. However, there are circumstances in which regulatory institutions recognize that AED side effects

can be reported directly by health care providers in a voluntary or even in a mandatory way. The management of pregnancy registries has to balance moral obligations towards respecting the autonomy of the mother and her informed consent with the public health interest to have safe AEDs. As pregnancy registries do not offer the same strength of medical evidence as randomized controlled clinical trials, the public regulatory institutions should communicate rather cautiously. They usually have to consider a bundle of factors for labelling AED in pregnancy, based on the number and seriousness of events reported, the evaluation of a possible causality following the intake of AEDs, and the balance of maternal benefit versus foetal risks. Therefore, the medical and research epilepsy communities are responsible for creating the best possible quality pregnancy registries, including the appropriate women with epilepsy to gain valid scientific information.

In addition to the well established requirements of good clinical practice and legal obligations, **Table 1** proposes an ethical approach to guide the conduct for pregnancy registries, which identifies the balance of powers between mother, other members of the family, healthcare providers and public or private institutions.

The main values are related to autonomy, privacy, trust, common good and justice. Additionally, the concept of agency strengthens the importance of knowledge and information in order for the women to exercise their autonomy and for the health care professionals to act in a responsible way. Agency is considered as the freedom to achieve whatever the individual, as a responsible being, decides to achieve [17].

Education and information are crucial at all levels: i) for women with epilepsy in order for them to consent to participate in the pregnancy registry and to accept a long-term follow-up; ii) for the partner to support the mother's commitment to the registry and the child's medical and psychological follow-up; iii) for the different health care providers to share data and coordinate the care in a transparent and confidential way; iv) for public health administrators publishing guidelines to assure the protection of women and foetus even if they go against commercial interests.

Awareness and knowledge of the impact of epilepsy and AED on pregnancy have been assessed in women with epilepsy. Their knowledge was found to be insufficient [18]. There is a clear demand for more information, especially in women aged less than 35 years [19]. A qualitative approach with focus groups identified this need for information particularly as most of the women concerned had an unintended pregnancy [20]. These findings emphasize the importance to develop preconception counselling for women with epilepsy and their partners, and to foster shared decision-making [21].

Health care professionals are not only accountable for informing women and their partners, but they should also work in a coordinated network to guarantee the confidentiality of the registry data, the informa-

Table 1: Ethical considerations for the inclusion of women with epilepsy in pregnancy registries.

Cluster of data to be collected during the lifespan of the pregnancy registry	Persons concerned in first place	Health care providers involved	Issues for inclusion	Ethical concepts
Epilepsy disease and pregnancy: history, former pregnancies, comorbidities, evolution during pregnancy, complications of pregnancy or epilepsy	Mother	GP Neurologist Obstetrician Mid-wife	Consent: Mother Information Confidentiality Data sharing Coordination	Autonomy Privacy Trust
Exposure to AED: Nature, modification (type or dosage), compliance, combination, other treatment non-AED (e.g. folic acid)	Mother	GP Neurologist Obstetrician Biologist (laboratories)	Consent: Mother Information Coordination Public health interests Private (Pharma) interests	Autonomy Common good Trustworthiness Transparency Conflict of interests
Foetus: development, death, major malformations, minor malformations	(Foetus) (Mother/ Parents)	Obstetrician Paediatrician (Radiologist/images)	Parent Information Data sharing Confidentiality Linkage to birth registries Dissemination of results Compensation of side effects	Agency / accountability Justice
Child: malformations, cognitive disorders, other disorders	Child (Parents, Family)	GP Paediatrician Psychologist School teacher	Parent Information and consent to follow-up Coordination Access to data Dissemination of results Compensation of side effects	Autonomy Agency / accountability Privacy Justice
All	Mother and future mothers with similar conditions	Registry administrator Steering committee (governance)	Confidentiality Transparency Scientific validity Data access Feedback to health care providers and regulators Funding Conflict of interest Publication of results	Trustworthiness Prudence Accountability Conflict of interests Justice

tion given for the benefit of the mother, and to safeguard the scientific value of the registry. The registry steering committee should moreover behave with prudence in the interpretation and dissemination of the registry results. Furthermore, transparency and trust between participants should be maintained during the lifespan of the registry, and facilitate the inclusion and retention of the highest possible number of mothers and children.

In addition to the necessary defence of the common good of managing future pregnancies in women with epilepsy and gaining knowledge about the safety profiles of AEDs, public institutions should respect justice and support social acceptance of the unpredictable future of mothers with epilepsy, their foetus and their child. Justice can be seen as the main argument for sup-

porting inclusion of women in the registry, if they experience the support of the community and feel encouraged to reciprocally contribute to pregnancy registries.

Conclusion

This brief review on epilepsy and pregnancy has identified the difficulty of appropriately balancing the benefit of the epilepsy treatment for pregnant women, whilst at the same time protecting the foetus and preserving a normal development for the new-born. Clinical research is difficult to undertake with pregnant women, who will typically be considered as “vulnerable subjects”. Pregnancy registries offer a good observational research alternative, as long as they not only fol-

low good clinical practice and legal obligations, but also include the appropriate population for a long enough period. This paper proposes ethical considerations able to guide the inclusion of women with epilepsy in pregnancy registries. This approach aims to strengthen the respect for patients' autonomy and privacy, and promotes the common good of future pregnant patients and the foetus. In practice, patients' agency and healthcare professionals' accountability should be developed further. This can be achieved firstly through the education of women with epilepsy, secondly through sharing information in a transparent and confidential way within a coordinated network of healthcare providers. Finally, this will also require just institutions able to react quickly, disseminate findings with prudence and assure social protection in case of deleterious effects of antiepileptic treatment for the mother or foetus.

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