IMPACT OF CLINICAL PHARMACIST INTERVENTION BY USING DIGITAL TECHNOLOGY ON CLINICAL OUTCOMES AMONG PREGNANT WOMEN: RATIONALITY OF DRUG PRESCRIPTIONS AT A TERTIARY HOSPITAL IN KELANTAN

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by

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LIST OF ABBREVIATIONS

ACE-I	Angiotensin-converting enzyme inhibitor
ADEC	Australian drug evaluation committee
ANC	Antenatal clinic
ARBs	Angiotensin-ii receptor blockers
ASHP	American Society of Health System Pharmacists
ATC	Anatomical therapeutic classification
BNF	British national formulary
CAPE	Center for the advancement of pharmacy education
DM	Diabetes mellitus
DIC	Drug information center
DVD	Digital video disc
FASS	Swedish catalogue of approved drugs
GDM	Gestational diabetes mellitus
HUSM	Hospital Universiti Sains Malaysia
ICD-10	International classification of diseases-10
ICS	Inhaler corticosteroids
JAMA	Journal of the American medical association
JEPeM	Jawatankuasa etika penyelidikan manusia
INRUD	International network for rational use of drugs
IOM	Institute of medicine
KSA	Kingdom of Saudi Arabia
MGL	Morisky-green-levine
NSAIDs	Non-steroidal anti-inflammatory drugs
OTC	Over the counter
PIH	Pregnancy-induced hypertension
QR	Quick response
RCT	Randomized control trial
RIGHT	(Right patient, Right drug, Right dose, and Right cost)
SANE	(Safety, Affordability, Need, and Efficacy)
SBSQ	Set of a brief screening questionnaire

SMS	Short messages services
SPSS	Statistical package for the social sciences
UAE	United Arab Emirate
URTIs	Upper respiratory tract infections
USA	United State of America
USFDA	The United States food and drug administration
UTIs	Urinary tract infections
VAS	Visual analogues scale
WHO	World health organization

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KESAN INTERVENSI AHLI FARMASI KLINIKAL DENGAN MENGGUNAKAN TEKNOLOGI DIGITAL TERHADAP HASIL KLINIKAL DALAM KALANGAN WANITA MENGANDUNG: RASIONAL PRESKRIPSI UBAT-UBATAN DI HOSPITAL TERTIARI DI KELANTAN

ABSTRAK

Wanita mengandung memerlukan penjagaan farmaseutikal dan perubatan yang khas untuk mengelakkan sebarang bahaya dan kecacatan bayi. Kajian ini mempunyai tiga tujuan utama. Tujuan pertama adalah untuk mengukur kesan program pendidikan melalui penggunaan WhatsApp terhadap wanita mengandung mengenai pengetahuan, tanggapan, amalan, kepatuhan pengambilan ubat-ubatan, dan literasi kesihatan mereka. Hal ini adalah tambahan selain untuk mengukur kesan program pendidikan yang disesuaikan terhadap hasil klinikal (tekanan darah, nadi, profil gula darah, berat badan, dan proteinuria) wanita mengandung yang menghidapi diabetes dan/atau hipertensi. Tujuan kedua adalah untuk mengukur pengetahuan dan amalan pakar penjagaan kesihatan, serta tanggapan mereka terhadap risiko teratogenik ubat-ubatan yang digunakan semasa mengandung. Tujuan terakhir adalah untuk menilai corak preskripsi ubat-ubatan yang rasional di jabatan ginekologi dengan menggunakan petunjuk preskripsi ubat-ubatan WHO/INRUD. Kaedah Kajian: Terdapat tiga kaedah yang digunakan dalam kajian ini. Percubaan terkawal secara rawak digunakan untuk menilai impak program pendidikan terhadap wanita mengandung. Seramai 800 orang pesakit secara rawak dibahagikan kepada kumpulan intervensi dan kumpulan kawalan. Dengan menggunakan aplikasi WhatsApp, program pendidikan telah diedarkan kepada semua peserta manakala program pendidikan yang disesuaikan hanya diedarkan kepada pesakit mengandung yang menghidapi diabetes dan/atau hipertensi. Semua domain pengajaran diukur dengan menggunakan soal selidik yang disahkan dan borang pengumpulan data sebelum dan selepas tamat pendidikan. Soal selidik yang disahkan telah diedarkan kepada semua ahli penjagaan kesihatan dan ahli farmasi di jabatan ginekologi untuk mengukur pengetahuan, tanggapan, dan tanggapan terhadap risiko teratogenik

ubat-ubatan yang digunakan semasa mengandung. Akhir sekali, sejumlah 741 preskripsi dipilih secara rawak daripada fail perubatan pesakit dan dianalisis dengan menggunakan petunjuk preskripsi ubat-ubatan WHO/INRUD. Analisis data yang sesuai dilakukan dengan menggunakan SPSS versi 22. **Keputusan:** Terdapat kesan positif yang signifikan terhadap program pendidikan khusus (P<0.001) pada profil gula darah pesakit dan tekanan darah diastolik. Begitu juga, penambahbaikan yang ketara (P<0.001) telah dilihat dalam kebiasaan peserta dengan klasifikasi risiko teratogenik dadah di samping pengetahuan, persepsi, kepatuhan, dan amalan mereka. Walau bagaimanapun, walaupun majoriti kakitangan profesional kesihatan menunjukkan tahap pengetahuan yang tidak mencukupi mengenai ubat-ubatan yang digunakan semasa kehamilan, pakar perubatan dan ahli farmasi menunjukkan tahap pengetahuan yang agak baik. Selain itu, hanya 61 (27.6%) kakitangan profesional kesihatan yang sentiasa merasa yakin apabila menetapkan/menasihatkan ubat semasa kehamilan dan hanya 64 (29.1%) daripada mereka yang selalu meminta wanita hamil mengenai penggunaan ubat-ubatan yang ditetapkan semasa dan sebelum kehamilan. Selain itu, beberapa penunjuk preskripsi WHO didapati berada dalam lingkungan normal manakala peratusan pertemuan dengan antibiotik dan peratusan pertemuan dengan suntikan yang kurang daripada jangkaan normal (17.67%) dan (8.23%) masing-masing. Selain itu, sebilangan besar ubat yang ditetapkan (24.5% dan 34.0%) adalah kategori kehamilan USFDA, A dan B, masing-masing. **Kesimpulan:** Pendidikan pesakit menggunakan WhatsApp terbukti berkesan dalam meningkatkan pengetahuan, persepsi, amalan, pematuhan dadah, tekanan darah diastolik dan profil gula darah. Ahli sakit puan dan ahli farmasi mempunyai pengetahuan yang baik terhadap penggunaan ubat semasa kehamilan. Walau bagaimanapun, hanya sebilangan kecil penyedia penjagaan kesihatan yang yakin apabila menetapkan / memberi nasihat kepada wanita hamil dengan ubat-ubatan. Selain itu, kebanyakan ubat yang ditetapkan adalah rasional dan selamat dan semua petunjuk WHO/INRUD berada dalam julat normal kecuali dengan peratusan pertemuan dengan antibiotik dan ubat suntikan yang kurang daripada jangkauan normal. Penemuan kajian ini mendedahkan bahawa masih ada ruang untuk penambahbaikan dan lebih banyak perhatian daripada kakitangan kesihatan yang diperlukan mengenai petunjuk tersebut.

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ABSTRACT

Pregnant women need unique pharmaceutical and medical care to avoid any harmful and birth defects. Three main objectives were assessed in this study which were measuring the impact of an educational program using WhatsApp on pregnant women knowledge, perceptions, practice, drug adherence, health literacy, and diabetic and/or hypertensive participants' clinical outcomes as well as measuring healthcare professionals' knowledge, practice, and teratogenicity risk perceptions towards medications used during pregnancy. The last aim was to evaluate the rational drugs' prescribing pattern at the gynecology department using WHO/INRUD drug prescribing indicators. **Methodology**: Three methodologies were used in this study. A randomized control trial was used in assessing the impact of an educational program on pregnant women. Where 800 patients were randomly divided into intervention and control groups. By using WhatsApp application, an educational program was sent to all participants whereas a tailored educational program was sent only to pregnant patients with diabetes and/or hypertension. All study domains were measured using a pre-validated questionnaire and data collection sheet before, after and at one month after the end of the education. A pre-validated questionnaire was distributed to all healthcare providers and pharmacists at the gynecology department to measure their knowledge, perceptions, and teratogenicity risk perceptions towards medications use during pregnancy. Finally, a total of 741 prescriptions were randomly selected from patients' medical files and analyzed using WHO/INRUD drug prescribing indicators. Appropriate data analysis was made using SPSS version 22. **Results**: There were strong positive

significant impacts of the tailored educational program ($P<0.001$) on patients' blood sugar profile and diastolic blood pressure. Similarly, significant improvements ($P<0.001$) were noticed in participants' familiarity with the classification of the drug teratogenicity risks in addition to their knowledge, perceptions, adherence, and practice. However, although the majority of health professional staff showed an inadequate level of knowledge regarding the medications used during pregnancy, specialist physicians and pharmacists showed a relatively good level of knowledge. As well, only 61(27.6%) of health professional staff always feel confident when prescribing/advising drugs during pregnancy and only 64(29.1%) of them always asking pregnant women about the use of prescribed medications during and before pregnancy. Moreover, some WHO prescribing indicators were found to be in the normal range while the percentage of encounters with antibiotics and percentage of encounters with injections which were less than the normal range (17.67%) and (8.23%), respectively. As well, substantial proportions of prescribed drugs (24.5% and 34.0%) belonged to USFDA pregnancy categories A and B, respectively

Conclusion: Patients' education using WhatsApp proved to be effective in improving pregnant women's knowledge, perception, practice, drug adherence, diastolic blood pressure, and blood sugar profile. Gynecologists and pharmacists had a good level of knowledge towards medicines' use during pregnancy. However, only a small percentage of health care providers were confident when prescribing/advising pregnant women with medications. As well, most prescribed medications were rational and safe and all of WHO/INRUD indicators were in the normal range except with the percentage of encounters with antibiotics and injection drugs that were less than the normal range. The findings of this study reveal that there is still room for improvement and more attention from health staff is required regarding those indicators.

CHAPTER 1

INTRODUCTION

1.1 Study Background.

Pregnancy is defined as "The period from conception to birth when developing fetus is carried in women uterus." This period is divided into three trimesters; the first trimester includes the early three months of pregnancy (1-13 weeks) then the second trimester that consists of the next three months of pregnancy (14-27 weeks) and finally the third trimester which includes the later three months of pregnancy (≥ 28 weeks) (Gadisa & Guyo., 2014).

The first trimester is considered as the most critical period that causes structural malformations to the fetus because most of the drugs cross the incomplete placenta barrier, where organogenesis happens during this trimester (Gilbert., 2010) whereas second and third trimesters are relatively safer (Malm, 2005). However, this is not a rule for all drugs due to some of them have a harmful effect even during the third trimester of pregnancy. Moreover, some drugs may kill the fetus if they are taken within the first three weeks of fertilization or may not affect the fetus at all because the malformation is difficult to happen during this early period. This period is called "all or none" period(Kacew., 1994).

On the other hand, when pregnant women use medications during the embryo period (Organogenesis 3-10 weeks of gestational age) mainly when tissues and major organs of the fetus are structured, at this time, the harmful effects of medications on the unborn baby range from minor to major birth defects (Bánhidy, Lowry, & Czeizel., 2005).

According to Brent in 1986, human teratogen is defined as “a chemical drug, metabolic state, physical agent or psychological alteration during development that produces a permanent pathologic or pathophysiologic alteration in the offspring at exposures or circumstances that commonly occur”(Brent., 1986).

The World Health Organization (WHO) defined a birth defect as “structural or functional abnormalities that are commonly seen at birth” (WHO 2010). Birth defects have different synonyms as congenital disorders, congenital malformations, or congenital anomalies.

The minor birth defects mean slightly abnormal physical deviation than normal neonate where medical or cosmetic treatment is unnecessary such as hypospadias(Koren, Pastuszak, & Ito., 1998). However, major birth defects which may include many severe abnormalities that are seen on birth time such as functional, anatomical and metabolic defects or abnormalities observed in the future as a physical and mental disability which in some cases lead to death (WHO., 2016) and need medical or surgical interventions such as neural tube defects and spina bifida (WHO., 2009) .

Unfortunately, babies live with birth defects have a high risk of developing physical, mental and social difficulties which do not improve even by using medications or other supportive interventions. It is important to mention that; anatomical malformation or physical disruptions are more acceptable to be linked to teratogenic risks of drugs than functional or character changes in the newborn or the childhood stage (Wilson et al., 2007).

In 1930, malformation of babies was connected to x-ray exposure during pregnancy and before this, there was a concept that the uterus can protect the unborn baby from any external harmful substances(Buhimschi & Weiner., 2009).

In the 1960s, the catastrophic event happened when pregnant women used thalidomide during pregnancy for morning sickness. Thalidomide catastrophe caused congenital abnormalities for 6000-8000 neonates in addition to many cases of abortions and fetal deaths (Kalter, 2003; Lenz., 1988). At that time, the medical community believed that thalidomide was safe during pregnancy because it does not cross the placenta. But when the teratogenic impact happened, the medical and general population have turned to overestimate the teratogenic risk for many drugs. Hypothetically, even if the drug does not cross the placenta, it does not mean it is safe drug because merely may destroy the placenta (Koren et al., 2010).

However, determination of the right level of teratogenic risk factors would be very difficult due to many reasons such as low incidence rate of significant teratogenicity caused by drugs (less than 1%) which are relatively small to determine the exact risk, high prevalence of taking medications during pregnancy, and high percentage of pregnant women with polypharmacy which make it difficult to memorize these medications(Sachdeva, Patel, & Patel., 2009).

Although the percentage of teratogenic effects caused by the use of some drugs during pregnancy is low, there are other different sources of risks which may cause teratogenic effects as 9% of these teratogenic effects are related to (diseases, alcohol, and infections), 20 – 25% are related to genetic disorders and around 65% are related to unknown causes (Webster & Freeman., 2001).

However, even if a pregnant woman used teratogenic drugs during pregnancy, it is not necessary that her unborn baby will have congenital abnormalities. This is because teratogenic effects depend on many factors such as drug dose (some drugs are safe at low doses, but teratogenicity occurs only when the dose increases to more than the threshold level), route of administration (topical administration has less harmful

effects than systemic), duration of treatment (long duration increases the toxicity), and gestational time upon use of the medications (the first trimester is the most critical period for teratogenicity)(Fisher, Rose, & Carey., 2008)

Moreover, because pregnant women are excluded from most clinical trials due to the ethical and legal considerations, most information regarding drugs' safety during pregnancy comes from animal studies, epidemiological studies, and case reports with limited information regarding the safety/risk of using drugs during pregnancy(Bertollini, Pagano, & Mastroiacovo., 1993).

The core concept of pregnant women is that drugs are unsafe during pregnancy which may cause harmful effects on their unborn babies (Sachdeva et al., 2009). This belief by pregnant women might come from different sources such as healthcare providers, internet, midwives (Grimes, Forster, & Newton., 2014) and in many cases comes from the medicines package labels when a standard statement that usually written in the leaflet which is "use a drug if the benefit outweighs the risk" this vague and general statement may lead to overestimating the teratogenic risk perception by pregnant women (Bjerrum & Foged., 2003).

Additionally, the ambiguity of some scientific evidence-based references in terms of medications use during pregnancy such as British National Formulary (JFC, DAG, & BNF., 2016) statement "Drugs should be prescribed during pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester….". Also, BNF advised that all previously prescribed medications during pregnancy have the priority than the new ones which means that all new medications or those which were not used earlier during pregnancy, should be avoided if possible (JFC et al., 2016).

Diabetes Mellitus (DM) is a medical condition where an increase in glucose blood level occurs due to abnormal metabolism of glucose, and if this increase happens during pregnancy and disappears after delivery, it is called Gestational Diabetes Mellitus (GDM) (ADA., 2004). In 2015, pregnant women who had hyperglycemia during pregnancy was 20.9 million, and GDM represented 85.1% of these cases (IDF., 2015).

GDM has many maternal risks such as increasing the chance of cesarean section, preterm labor, and development of Type (II) DM. Also, GDM may cause a fetal risk such as congenital malformation, perinatal death, shoulder dystocia, and fetal hyperglycemia(Fahmy & Bassuoni, 2015; Madhuvrata, Govinden, Bustani, Song, & Farrell., 2015).

Controlling the blood glucose levels is very important since many studies claimed a strong relationship between congenital disabilities and control of blood sugar profile during the early period of pregnancy (first three months).

According to a meta-analysis on 35 scholarly articles published between January 2006 and January 2008. The researchers found that women with diabetes were associated with an increased risk of maternal and fetal complications. However, to decrease the risks of these complications in diabetic women, blood glucose must be normalized before conception through preconception counseling. HbA_{1c} levels were reported to be significantly lower in women who received preconception counseling than in those who did not receive the counseling (Charron, Hannan, Fischl, & Slocum., 2008; Reece & Homko., 2000).

As well, achieving optimal HbA_{1c} levels before conception through preconception counseling continued to be associated with significantly lower HbA_{1c} levels from conception up to 24 weeks gestation; it was also associated with decreased

risk of spontaneous abortions and diabetic embryopathy (Charron, Hannan, Fischl, & Slocum., 2008; Reece & Homko., 2000).

Furthermore, hypertension disease during pregnancy is considered as one of the primary causes of more than half of maternal deaths during 2003-2009 (Say et al., 2014). WHO reported that a minimum of one pregnant woman dies every seven minutes due to hypertension complications during pregnancy and each year around 76000 women die due to preeclampsia and other related hypertension disorders(Kuklina, Ayala, & Callaghan., 2009).

Hypertension complications could affect different organ systems and harm both pregnant and unborn babies. These complications include increasing low birth weight due to fetal growth retardation or preterm labor(Muhammed et al., 2014).

In addition, many factors could play a major role in patients' treatment success, such as patients' adherence to treatment, health literacy and healthcare professionals' knowledge and rationale prescribing patterns.

WHO defines adherence as, "A term which is often used interchangeably with compliance, as the extent to which a person's behavior taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (WHO., 2003).

Non-adherence occurs when a patient does not initially fill or refill a prescription, discontinues a medication before therapy is completed, or does not follow instructions for dosing and schedule.

WHO mentioned that the primary challenge in the management and treatment of patients with chronic diseases is non-adherence to drugs. WHO quoted the statement by Haynes et al., that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in

specific medical treatments" (WHO., 2003). Because even the best-prescribed drugs would not give the appropriate efficacy if they are not taken properly and it is good to remember that "Drugs do not work in patients who do not take them" (Bonaccorso & Sturchio., 2003).

There are two types of medications non-adherence:

Type I: 'Intentional non-adherence' or 'intelligent non-adherence' means that patient decides not to take the drugs as prescribed after knowing the benefit/risk ratio or the cost of drugs.

Type II: 'Unintentional non-adherence' means that the patient does not take the drugs as prescribed due to different reasons such as forgetfulness, inadequate knowledge or physical problems (Wroe., 2002).

The main prevalent types of non-adherence among pregnant women were forgetting to take the dose, reducing the dose or entirely discontinuing the drugs (Barbour, Macleod, Mires, & Anderson, 2012; Sawicki et al., 2011). The nonadherence has a negative impact on clinical outcomes of chronic diseases such as diabetes and hypertension.

It is believed that proper health literacy could increase patients' safety and the chances of treatment success. Health literacy is defined as ''The degree to which individuals have the capacity to obtain, process, and understand basic health information and services required to make appropriate health decisions'' (Nielsen, Panzer, & Kindig., 2004).

However, a high educational level does not mean adequate health literacy inevitably (Lupattelli, Picinardi, Einarson, & Nordeng., 2014), but low education level can be considered as an essential factor associated with low health literacy(Cho, Plunkett, Wolf, Simon, & Grobman., 2007).

Multiple factors may affect health literacy such as general literacy (the ability of reading, writing and understanding the text), individual experience, difficulty or simplicity of information, a way of communication, and cultural restrictions (AMAF., 2012).

According to a report by the Institute of Medicine (IOM), it was claimed that around 50% of all American adults face problems with using and understanding health information. Additionally, the IOM report mentioned that "efforts to improve quality, reduce costs, and reduce disparities cannot succeed without simultaneous improvements in health literacy" (Lynn., 2004).

Adequate health literacy can assist pregnant women in understanding and following the required lifestyle plan (exercise and diet habits) and controlling blood sugar levels(McLaughlin, 2009). As well, health literacy makes them aware about the prenatal screening tests for birth defects, able to notice any medical problems, seek healthcare at the right time, right place, assist them to understand the danger signs during pregnancy and following up to solve health-related problems.

Patients' adherence and a good level of health literacy are considered as one side of treatment success while rationale drug prescribing by healthcare professionals is considered an equally important side.

However, the variability of educational backgrounds among healthcare professionals, differences in their practice settings, and various information resources would result in different perceptions towards medications which could be reflected in their practice. As lacking or conflicting information regarding medicines' uses during pregnancy is considered a big problem, the amplification of medicines' teratogenic risk by healthcare professionals may cause severe harmful consequences for both

mothers and babies. For instance, irrational of drug prescription, pregnant abortion and may increase pregnant women's anxiety (Acs, Puho, Banhidy, & Czeizel., 2005).

WHO/International network for rational use of drugs (INRUD) core drug prescribing indicators can assist healthcare providers in achieving a higher level of rational prescribing of drugs through measuring specific criteria and parameters in prescriptions such as average number of prescribed drugs per prescription, percentage of the drugs which were written by generic name, rate of antibiotic and injections prescribed per patient and adherence level to formulary/essential drug list (WHO., 2002).

In 1985, WHO defined rationale use of drugs as "The rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time and at the lowest cost to them and their community"(WHO., 1987).

WHO reported that nearly half of all medications are irrationality dispensed, prescribed or sold (WHO., 2011). As a general rule, all the medications are preferred to be prescribed with small doses for a short time and avoid polypharmacy to minimize the side effects and drug-drug interactions(Salwe, Kalyansundaram, & Bahurupi., 2016).

America, Austalia, and Sweden countries were developed drug classification systems to assist the rationality of drug prescription during pregnancy. The most known classification systems are the United States Food and Drug Administration (USFDA), the Swedish Catalogue of Approved Drugs (FASS) and the Australian Drug Evaluation Committee (ADEC) which also has a classification system (Addis, Sharabi, & Bonati., 2000).

The USFDA classification system is widely used in many countries compared with other classification systems. As well, this system is used at HUSM. Thereby, the researchers in this study selected the USFDA system.

However, the utility of USFDA, FASS and ADEC classification systems is restricted because of the low level of consistent classification between them where only 26% for a total of 236 commonly used drugs and all of them profoundly make simple classification to the drugs and majority of medications under a neutral category that leads to misinterpretation or oversimplification of the medication's risk.

As well, not all drugs were classified because either some of them were not approved by these systems or they might be launched and approved in any other different countries. Also, the categorization of drugs is modified according to pregnancy trimester and subgrouping even if the drugs have the same pharmacology class.

Nevertheless, these classification systems can be used as therapeutic guidance regarding the safety/toxicity risks of medications during pregnancy.

It is important to mention that; the latest publication regarding the amount of data available concerning the safety/toxicity risks of drugs used during pregnancy was stated as not available for approximately 73% of drugs (Adam, Polifka, & Friedman., 2011).

One of the most known teratogenic drugs is isotretinoin that causes cleft palate, neural tube defects, and thymic aplasia if used during pregnancy at any gestational age. However, other drugs such as tetracycline could impaired bilirubin conjugation if used during third gestational age (Wilson et al.,2007).

Patients education and rational drug prescribing are considered the main pillars that play a critical role in improving patients' quality of health (Sivasakthi,

Senthilkumar, Rajendran, Anudeepa, & Narayanan., 2011) and patients education is the main practice in pharmaceutical care. Nevertheless, there are limited available studies regarding the pharmacist's role in pregnant women education or counseling (Samuel & Einarson., 2011).

According to the Center for the Advancement of Pharmacy Education, pharmacists are expected to have an essential role in providing medical information for patients and their caregivers and in educating a wide range of community on the rational use of medications (Medina et al., 2013) and a good role in improving the clinical outcomes of different disease (Cani, Lopes, Queiroz, & Nery., 2015; Javedh, Jennifer, Laxminarayana, & Bhat., 2016)

Patients education is the process of enhancing patients' information and knowledge to motivate them for improving and maintaining their health. Patients education should be conducted in highly effective ways. According to the American Society of Health System Pharmacists (ASHP), there are four steps to efficient patient counseling which are: (1) good caring relationship; (2) evaluating patient's knowledge, perception, and mental capacity; (3) providing visual tools with verbal information; (4) confirming the patient's understanding (ASHP., 1997).

Patients education is not basically transferring certain information to patients and then asking them to follow up the instructions. However, effective education could be achieved by motivating patients for education by using simple, convenient, and enjoyable educational tools (Jahromi., 2016).

While some of the healthcare providers use printed materials to explain the diseases or drug information to their patients, still most patients cannot understand these printed materials because they need simple, brief, and illustrate the concepts by photos (Safeer & Keenan., 2005). Thus non-printed materials such as video, audio,

and image could be the best solution for patients with low health literacy and also for patients with adequate health literacy who do not prefer reading(Tehrani et al., 2007). Furthermore, pregnant women with low health literacy usually seek information from different resources such as radio, television, family or friends but often avoid printed materials(Akbarinejad, Soleymani, & Shahrzadi., 2017).

Today, people are living in an era of technology that reshaped their life in different ways where no one might have ever predicted. The word technology was derived from the Greek word “techno” which means knowledge of the way, skills and “logo” which means science, learning (Stosic., 2015).

Utilizing technology in education can make it more attractive, enjoyable and cost-effective. This is mainly due to the additional features of technology over the classical way of education. As well, technology provides different formats, methods, and strategies of interventions that encourage active learning and thereby, increase the knowledge retention among learners.

Animations and images can easily explain complex medical concepts to pregnant women and increase the likelihood of paying attention. Video has rich forms of audio, texts, and images profoundly impact remembering more information (Rockwell & Singleton., 2007). Using video as an educational technology method is preferred and an efficient way as found in many peer-reviewed published articles (Ali et al., 2012; Kim, Mohammad, Coley, & Donihi., 2015; Moore et al., 2015).

As well, mobile phones or smartphones are great tools for improving education (Short, Lin, Merianos, Burke, & Upperman., 2014). Using mobiles in healthcare delivery is called mobile health or m-Health. Mobile phones are widely used among the general public. Smartphones are personal devices that prompted privacy. Utilizing smartphones give the ability to reach the target pregnant women immediately within a

short time so, pregnant women are more likely to read a message and take action right away. Smartphones with its incredible applications have changed many aspects of people's lifestyles (Dar et al., 2017). The invention of smartphones makes a good chance for technology to be in daily clinical practice in different health areas because smartphones have access to download many useful medical and nonmedical applications (like WhatsApp) that assist health staff in doing their jobs. Moreover, smartphones have many specifications such as portability, ability to update, communication options, and simplicity which led to the acceptance and widespread of smartphones (Giordano & Koch., 2017).

WhatsApp is one of the most commonly used social media application which has been downloaded in more than 40 countries and approximately 1 billion videos, 4.5 billion photos, and 55 billion messages are sent or shared per day by 1 billion daily active users in the world (WhatsApp Inc, 2018). WhatsApp has many amazing functions that explain its widespread success such as sending or sharing many messages, photos, videos, and recorded voice calls without any cost [not like short messages services (SMS)], and nearly available for all smartphones.

Furthermore, WhatsApp users can use the same Wi-Fi network or mobile data plan used for email or browsing, so it is cost-effective and reliable (Giordano & Koch., 2017). In Malaysia, using WhatsApp is a very suitable way because cell phones are widely used conveniently across all population ages and classes.

1.2 Problem Statement.

Traditional patients' education and counseling methods might face many challenges, barriers, and limitations which could affect the quality of the provided services. These drawbacks might result due to the crowded waiting areas, time limitations, patients' lack of emotional preparation, lack of privacy places, and a shortage of health staff (Laif, Ahmad, Naqvi, & Ahmad., 2017).

In 2012, the rates of diabetes mellitus and hypertension disorders among pregnant women in Kelantan (area of the present study), were 9.8% and 3.52%, respectively. (NOR., 2012). Gestational diabetes mellitus has many maternal and fetal risks. (Fahmy & Bassuoni., 2015; Madhuvrata et al., 2015).

Similarly, hypertension during pregnancy has many complications in pregnant women and fetuses. Therefore, hypertension is considered the most common cause of maternal mortality and morbidity (Roberts, Pearson, Cutler, & Lindheimer., 2003).

In Malaysia, the latest average incidence of hypertension in pregnancy-related maternal death was 13.6% from 1997 to 2008, and it was considered the fourth main cause of maternal mortality (NOR., 2012).

In Kelantan, using herbs is considered a common practice among pregnant women where the majority of them are using herbs without supervision(Kim & Lean., 2013). Regrettably, herbal products and over the counter (OTC) medicines might be harmful to pregnant women and their unborn babies more than prescribed drugs (Meadows., 2001). In addition to the frequent use of herbs during pregnancy, a recent Malaysian study found that 62% of pregnant women in Malaysia used at least one drug during their pregnancy period. (Jey, Siew, Rita, & Omar., 2017).

On the other side, adherence studies among pregnant women are limited and scattered with a high percentage of pregnant women nonadherent to their medicines particularly for chronic medications (Sawicki et al., 2011). Moreover, the non-adherence rate in the pregnant population is much higher than the general population (DiMatteo., 2004). Nonadherence may worsen the clinical outcomes, increase the hospitalization rates and therefore, increase healthcare costs.

According to a new systemic review in 2019, it was reported that Southeast Asian countries had limited health literacy(Rajah, Hassali, & Murugiah., 2019). Inadequate health literacy among pregnant women might prevent them from recognizing some significant prenatal issues such as the importance of medication compliance, planned pregnancy, and antenatal visiting(Cho et al., 2007).

As well, inadequate drug information or misestimation of drug teratogenicity risks by health professional staff have negative consequences such as incorrect pregnant consultations or inappropriate treatment for specific diseases during pregnancy, termination of the pregnancy, increase mother anxiety, increasing the possibility of teratogenicity, and losing the confidence between pregnant women and their healthcare providers (Finer & Henshaw, 2006; Nordeng, Ystrøm, & Einarson., 2010).

Lastly, irrational drug prescription may increase the cost of treatment and the harmful effects to the fetus which ends with raising the morbidity and mortality rates(WHO., 2011).

1.3 Study Justification.

Assessment of pregnant women's knowledge, perceptions, and practice towards medicines use during pregnancy is considered an important step to define their weakness, needs, and gaps. Thus, bridging these gaps through utilizing new technologies in developing an educational program for Malaysian pregnant women is considered an addition to serve them and a novel strategy. As well, finding intervention tools that assist in improving clinical outcomes of diabetic and/or hypertensive pregnant women and consequently improve their quality of life is very important.

Also, since there are limited studies about drug adherence and health literacy among Malaysian pregnant women and few studies have investigated the relationship between medication adherence and health literacy (Lupattelli, Picinardi, et al., 2014), developing and implementing this study is considered as essential research.

Moreover, health professional staff, mainly physicians, are considered the primary source of drug information for pregnant women. (Hämeen et al., 2013; Kassaw & Wabe., 2012) Therefore, misestimation of drug teratogenicity risk or inadequate drug information knowledge will negatively impact on the antenatal and pharmaceutical care processes. Thus, the researcher conducted this study to explore the healthcare providers' knowledge, teratogenic risk perceptions, and practices towards medications during pregnancy.

Finally, rational drug prescribing by healthcare providers with appropriate patient's counseling, (Sivasakthi et al., 2011) play a critical role in improving patients' quality of health. Moreover, in Malaysia, only a few pharmacoepidemiological studies assessed the potential of drugs teratogenicity during pregnancy (Jey et al., 2017) and the rational drug prescribing by healthcare providers using WHO core drug prescribing

indicators. (Kamaruzaman & Ibrahim., 2006). Thereby, it is aimed to evaluate drug prescribing pattern at the gynecology department. Up to our knowledge, this study is considered as novel research that analyzes drug prescriptions among Malaysian pregnant women by using WHO drug prescribing indicators.

The relationships between the study's components show in figure 1.1.

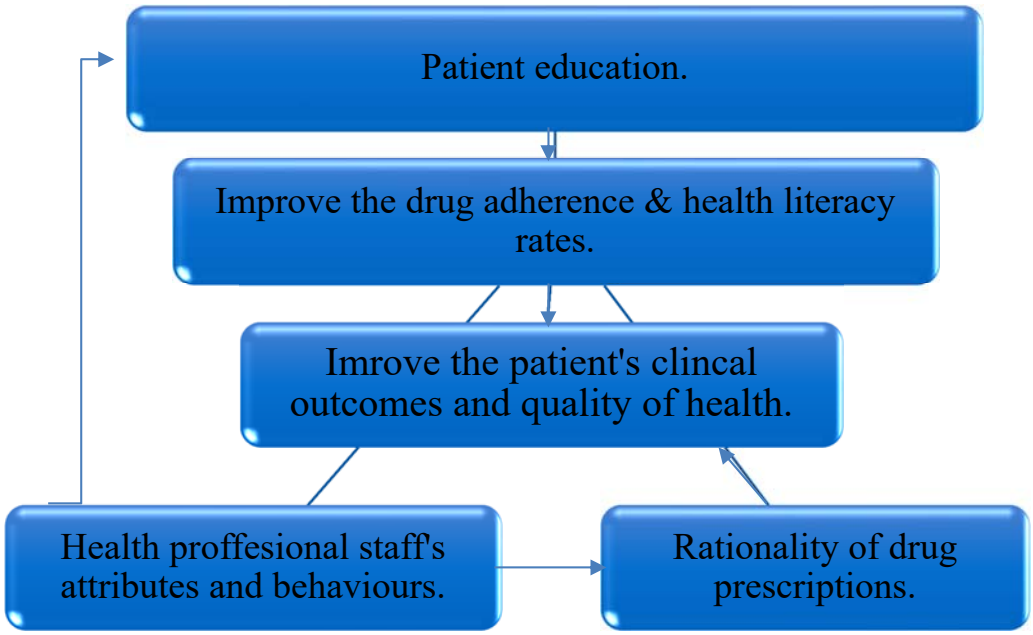

Figure 1.1: Conceptual framework of the study.

1.4 Study Significance.

Although this study is considered an innovative study that used a digital educational program among pregnant women. There is a growing body of studies that investigate the important role of technology on patients' education and counseling.

The investigators hoped that presence of educational program for pregnant women by using scientific evidence-based resources might improve their clinical outcomes, knowledge, perception, practice, drug adherence, health literacy, and assist them in getting accurate information in a more convenient, understandable, and acceptable method. Moreover, sharing the digital educational materials with other pregnant women will be persons than traditional printed materials and thereby, an unlimited number of pregnant women can get the benefits with a minimum cost and time. Also, the study provided educational materials and different measurements tools in Malay languages.

As well, exploring the drug teratogenic risk perceptions among pregnant women toward their medications may give healthcare providers a good baseline for covering the gap between pregnant women's teratogenic perceived and real risks through professional counseling.

Moreover, the information collected about health professional staff knowledge and perceptions toward the teratogenic risk of medications during pregnancy will help to increase their awareness and assist in designing continuous educational programs that could improve their knowledge and perceptions that can be integrated in their practice and consequently impact on patient's quality of life.

Furthermore, the researchers expect to give policymakers and healthcare professionals a baseline data on the current prescription pattern of medications to

pregnant women and the potentially harmful effects of these medications on those pregnant and their unborn babies. As well, researchers hope that the findings of this study can help in evaluating the standards of care for diseases among pregnant women in Malaysia.

Lastly, it is hoped that the outcomes of this study will help healthcare professionals to improve their rational prescribing for pregnant women to ensure their safety and to minimize the teratogenic risks. Thus, improving patients and newborn babies' quality of life.

1.5 Research Questions.

The following research questions were derived from this study:

- Would a tailored educational program by using digital technology improve clinical outcomes (blood pressure, blood sugar profile, body weight, proteinuria) among diabetic and/or hypertensive pregnant women in Kelantan, Malaysia?
- Would an educational program by using digital technology improve pregnant women's health literacy, knowledge, perceptions, practice, and drug adherence towards medicines in Kelantan, Malaysia?
- What are the knowledge, perceptions and practice levels of pregnant women regarding medications use during pregnancy in Kelantan, Malaysia?
- To which extent Kelantanese Malaysian pregnant women are adherent to their medications?
- What is the health literacy level of pregnant women in Kelantan, Malaysia?
- To which extent pregnant women in Kelantan, Malaysia, are able to classify drug teratogenic risks correctly?
- What are the knowledge, practice and teratogenic risk perceptions of healthcare staff towards medications use during pregnancy in Kelantan, Malaysia?
- To which extent physicians' prescriptions patterns are adherent to WHO/ INRUD drug prescribing indicators in Kelantan, Malaysia?

1.6 Research Hypothesis.

1. Null Hypothesis: The clinical outcomes of pregnant women (blood pressure. blood sugar profile, body weight, and proteinuria) will not be changed after receiving the tailored educational program

   Alternate Hypothesis: The clinical outcomes of pregnant women (blood pressure. blood sugar profile, body weight, and proteinuria) will be changed after receiving the tailored educational program.

2. Null Hypothesis: Levels of knowledge, Perceptions, practice, drug adherence, health literacy, and teratogenic risk perception, will not be changed after the educational program.

   Alternate Hypothesis: Levels of knowledge, Perceptions, practice, drug adherence, health literacy, and teratogenic risk perception, will be changed after the educational program.

3. Null Hypothesis: Health professional staff have poor knowledge, practice, and perceptions towards the medications use during pregnancy and don't have the ability to classify the drug teratogenic risk correctly.

   Alternate Hypothesis: Health professional staff have good knowledge, practice, and perceptions towards the medications use during pregnancy and have an ability to classify the drug teratogenic risk correctly.

4. Null Hypothesis: Drug prescribing patterns of physicians in gynecology clinics during pregnancy are not according to WHO/ INRUD indicators.

   Alternate Hypothesis: Drug prescribing patterns of physicians in gynecology clinics during pregnancy are according to WHO/ INRUD indicators.

1.7 Research Objectives

The researchers divided the research objectives according to the study phases.

The objectives of phase (I).

1. To identify the influence of tailored educational programs on clinical outcomes among diabetic and hypertensive pregnant women.
2. To identify the influence of the educational program on pregnant women's knowledge, perceptions, practice, medication adherence, health literacy, and drug teratogenic risk estimation.
3. To determine drug adherence and health literacy levels among pregnant women.
4. To evaluate the familiarity and ability of pregnant women to classify drug teratogenic risk.

The objective of phase (II).

1. To assess the knowledge, practice, and perceptions of health professional staff towards medications use during pregnancy.

The objective of phase (III).

1. To evaluate the rationality of prescriptions at the antenatal clinic using WHO/INRUD core drug prescribing indicators, and USFDA pregnancy categorization system.

CHAPTER 2

LITERATURE REVIEW

2.1 The teratogenicity rate in Malaysia.

A Malaysian study was designed to explore the prevalence of major malformations and related health problems in the state of Penang from 1999 to 2004 by using the international statistical classification of diseases (ICD-10) database. The researchers found an increase of congenital abnormalities in all regions in the state of Penang particularly in Barat Daya (Leela, Nagarajah, Stephen, & Hakim., 2013). These anomalies increased with an incidence rate of at least three per thousand births mainly from the nervous system, digestive system, genital organs, cleft lip, and cleft palate.

Another maternal screening study for congenital malformations was conducted in 1996 by the Health Technology Assessment Unit, Ministry of Health in Hospital Kuala Lumpur in Malaysia, found the incidence of significant congenital disabilities to be 0.91 %. Higher findings were reported by a study conducted in hospital Alor Star, state of Kedah between 1984-87, in which the incidence of malformation was found to be 1.52%. It is interesting to say that; the Ministry of Health Malaysia reported that 17.9% of neonatal deaths were due to congenital abnormalities(MOH., 2017).

It is essential to say that; there are many factors that might be lead to birth defects in Malaysia such as genetic predisposition, environmental pollution, and drugs. However, because a national system of screening and documentation for birth defects during both the antenatal and postnatal period is not yet in place and there is no a Malaysian birth defect registry, it is not certain whether there is an increase in the

incidence of birth defects and whether there is any significant association between these factors and birth defects and how much the percent of birth defects related to drugs (Boo., 2005).

2.2 Role of digital technology in education and healthcare systems.

Many studies reported the benefits of WhatsApp in communication and learning in the health field. Thirty articles that were published before January 2016 and relevant to WhatsApp were reviewed. The investigators found, with strong evidence, that WhatsApp can be used as a useful learning method for providing information to health professional staff and the general public. As well, WhatsApp was found to be a suitable communication method among health professional staff themselves as well as between them and the general population(Giordano & Koch., 2017).

In Malaysia, an exploratory study was conducted among students to explore their attitudes and perceptions regarding the use of WhatsApp as a learning tool. WhatsApp was found to successfully encourage and motivate students' learning and has beneficial effects on their behavioral attention(Mistar & Embi., 2016).

Findings from the previous study in Malaysia were concordant with two recently published studies in Britain and Turkey. Where WhatsApp was found to be a useful tool in problem-based learning among medical students and has a highly helpful role in educational technology, thus can be used as supportive learning technology (Cetinkaya., 2017; Raiman, Antbring, & Mahmood., 2017). Also, these results were parallel with a South African study (Willemse., 2015) where WhatsApp was found to be a useful tool among undergraduate nurse students to understand the practical and theoretical parts.