Study Protocol

**Prevalence and Determinants of Spontaneous Abortion in Northern Perak;
A 3 year Analysis**

Protocol number, version number and date:
Protocol number RSCH ID-23-01986-P5L , Version 1.0, 3rd April 2023

Name and Institution of Principal investigator:
Dr Rosilawati Abdul Rani, CRC Hospital Taiping

Name and Institution of Co-Investigators:
Sereevali a/p Muthuvadivelu , CRC Hospital Taiping
Norhairina bt Mohammed Khalid, PKD Kerian

Name and address of Sponsor:
Self funding

Study site/s:
PKD Kerian

Contents

List of Abbreviations

PKD	Pejabat Kesihatan Daerah
CI	Confidence Interval

Research Synopsis

Study title	Prevalence and determinants of spontaneous abortion in Northern Perak; A 3-year analysis
Study Population	Antenatal mothers booked at all health clinics in PKD Kerian from 2020-2022
Study Design	Cross sectional study
General Objective	To find out the prevalence and determinants of spontaneous abortion in Northern Perak from 2020-2022.
Specific Objectives	1. To determine the prevalence of spontaneous abortion in Northern Perak from 2020-2022 2. To find out the factors associated with spontaneous abortion in Northern Perak
Study endpoints/outcomes	1. Prevalence of spontaneous abortion in 3 years 2. Factors associated with spontaneous abortion
Sample Size	294
Study Duration	1st June 2023-31st May 2024

1.Background and Significance

Spontaneous abortion is one of the most common complications of pregnancy. It is defined as the expulsion or removal of an embryo or fetus from the uterus at a stage of pregnancy when it is incapable of independent survival (500gms or 22 weeks gestation). It may be spontaneous, or induced for medical or social reasons.[i]

The cumulative risk of abortion for weeks 5 through 20 of gestation ranged from 11 per 100 women to 22 per 100 women (11-22%).[ii] The prevalence is depending on the data sources. Data for abortion is not capture systematically in Malaysia as compared to stillbirth and under 5 mortality. Both data, are been used as a health indicator for the measurement of the health status of a country especially for its obstetric care management.

The risk of spontaneous abortion is multivariate and 50% have no identified causes. A cohort study of 4831 married women found that older age at the first marriage, and age at the first pregnancy on increased chance of spontaneous abortion.[iii] Women with lower income and educational attainment were inversely associated with the risk of spontaneous abortion[iv].

A case control study done in a hospital in Indonesia found that history of previous abortion, chronic maternal disease, anemia, advanced maternal age, multigravidity, and infection were associated with the occurrence of spontaneous abortion.[v] Among the genetic factors spontaneous abortion are associated with cytokine imbalance, allele polymorphisms, vascular endothelial growth factors, genotypes, chromosomal changes, congenital heart disease and vitamin D receptors.[vi]

Viral infections during pregnancy have a broad spectrum of placental and neonatal pathology. During the three years; 2020-2022, the spread of covid-19 virus were rampant. The incidence of abortion was increased by 25% during the COVID-19 pandemic in Turkey but the study did not demonstrate a causal link between abortion and SARS-CoV-2 infection.[vii]A study done by a group of researcher in UK found that women who are infected with SARS-CoV-2 in their first trimester may be an increased risk of an early abortion. [viii] However, no evidence of an increased risk for early pregnancy loss after Covid-19 vaccination.[ix]

Two important gaps remain in the literature regarding the frequency and distribution of spontaneous abortion. First, relatively little is known about the prevalence of spontaneous abortion at the population level. Second, the determinants of the problems are not as well understood. This study aims to address those issues in a small district in Northern Perak, hoping that the result will be a trajectory to a bigger study that can lead to a registry in future.

2. Objective
General Objective
To find out the prevalence and determinants of spontaneous abortion in Northern Perak from 2020-2022.
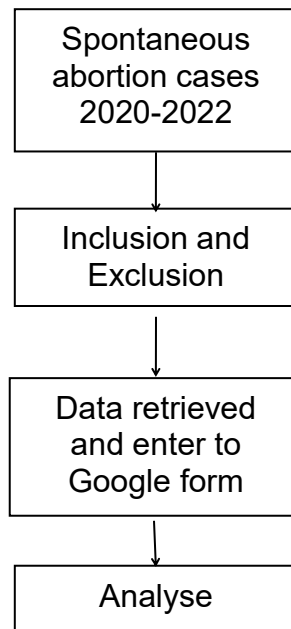
Specific Objectives
1.To determine the prevalence of spontaneous abortion in Northern Perak from 2020-2022
2.To find out the factors associated with spontaneous abortion in Northern Perak

3.Methodology
Cross sectional study-(retrospective data).

3.1 Study Type and Design
This study will be looking at all spontaneous abortion cases that were diagnosed in 2020 to 2022 (3 years duration). No follow up or meeting with patient needed. All data will be gathered from patient's antenatal cards (KIK/1(b)/96 (Pind.2020). The variables will include sociodemographic data, pregnancy and clinical related, outcome of the pregnancy, choice of family panning and how soon the subsequent pregnancy occur (if any). Since the duration was during Covid-19 pandemic, the date of first and second dose of Covid-19 vaccine will also be obtained. All data will be entered to google form. A training will be provided to those involve with data entry to ensure uniformity.

```
┌──────────────────┐
│   Spontaneous    │
│  abortion cases  │
│    2020-2022     │
└──────────────────┘
         │
         ▼
┌──────────────────┐
│  Inclusion and   │
│    Exclusion     │
└──────────────────┘
         │
         ▼
┌──────────────────┐
│  Data retrieved  │
│   and enter to   │
│   Google form    │
└──────────────────┘
         │
         ▼
┌──────────────────┐
│     Analyse      │
└──────────────────┘
```

3.2 Study Population
All antenatal cases booked at health clinics in PKD Kerian. Total antenatal cases booked under health clinics in PKD Kerian for the 3 years were 6041.

3.3 Inclusion Criteria
1. A case diagnosed as spontaneous abortion and underwent termination of pregnancy (medical or surgical)
2. Below 22 week of gestation

3.4 Exclusion Criteria
1. A Threatened abortion case
2. Booked outside PKD Kerian

3.5 Withdrawal Criteria
Not applicable

3.6 Sample Size

For the expected prevalence of 22%[ii,] the required sample size is 294 for the margin of error or absolute precision of ±5% in estimating the prevalence with 95% confidence and considering the potential loss/attrition of 10%. With this sample size, the anticipated 95% CI is (17%, 27%). This sample size is calculated using the Scalex SP calculator (Naing L, et. al., 2022).[x] Total cases diagnosed as abortion for the 3 years were 340. We will include all the cases, thus universal sampling will be applied.

3.7 Study Duration and Timeline
- Stage 1, data collection - 4 months
- Stage 2, data analysis - 2 months
- Stage 3, presentation and publication - 6 months

3.8 Study Visits and Procedures
All spontaneous abortion cases diagnosed in 2020 to 2022 will be retrieved.
All cases will be anonymous. Cases will be numbered accordingly. Data will be entered to Google form and will be transferred into SPSS for analysis according to stated objectives.
Data extracted will include
-Socio-demographic: Ethnicity,age, ethnicity and occupation, education level, smoking status (father)
-Pregnancy related-Gravida and para, POA at booking, POA at diagnosis of abortion, risk factors of pregnancy, consanguinity, tagging at booking, last child birth
-Outcome of the abortion: final diagnosis, medical or surgical intervention
-Family planning method, date of POA for subsequent pregnancy
-Covid-19 vaccination date, type of vaccine

3.9 Statistical Analysis Plan
The data analysis will be done using the SPSS version 22. Descriptive date will be expressed as mean ± standard deviation (SD) unless otherwise stated. One-way ANOVA will be used for analysis of normally distributed variables. Kruskal-Wallis ANOVA will be used for non-normally distributed data. Categorical data will be analyzed using Chi-square or Fisher's exact test. A value of $P < 0.05$ is considered statistically significant.

3.10 Risk and benefit to study participants
This study does not present any direct benefit to the patients. However, the study does provide a better understanding of spontaneous abortion in Malaysia.

3.11 Risk Benefit Assessment
There is minimal to none risk at all as all patient's data will be traced from their past history thus this study should be supported.

3.12 Ethics of Study
The study will be conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline.

3.13 Informed Consent/Assent Process
Not applicable. Since this is a secondary data using patients' record retrieve retrospectively, waiver of informed consent will be obtained.

3.14 Privacy and Confidentiality
Subject's names will be kept on a password-protected database and will be linked only with a study identification number for this research. The identification abbreviation instead of patient identifiers will be used on subject data sheets. All data will be entered into a computer that is password protected. On completion of study, data in the computer will be copied to a external hard disk and the data in the computer erased. External disk will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The external hard disk and data will be destroyed after that period of storage.

3.15 Conflict of Interest
The investigators declare they have no conflict of interest.

3.16 Publication Policy
No personal information will be disclosed and subjects will not be identified when the findings of the survey are published.

3.17 Termination of Study
Study will be terminated if ordered received from Pejabat Kesihatan Daerah or other relevant authority.

References

i Guideline On Termination Of Pregnancy (Top) For Hospitals In The Ministry Of Health Malaysia

ii Ammon Avalos L, Galindo C, Li DK. A. Systematic review to calculate background miscarriage rates using life table analysis. Birth Defects Res A Clin Mol Teratol. 2012 Jun;94(6):417-23. doi: 10.1002/bdra.23014. Epub 2012 Apr 18. PMID: 22511535

iii Moradinazar M, Najafi F, Nazar ZM, Hamzeh B, Pasdar Y, Shakiba E. (Lifetime Prevalence of Abortion and Risk Factors in Women: Evidence from a Cohort Study. J Pregnancy. 2020 Apr 27;2020:4871494. doi: 10.1155/2020/4871494. PMID: 32395342; PMCID: PMC7201453.

iv Zheng, D., Li, C., Wu, T. et al. Factors associated with spontaneous abortion: a cross-sectional study of Chinese populations. Reprod Health 14, 33 (2017). https://doi.org/10.1186/s12978-017-0297-2

v Safira Z. Risk Factors Associated with Spontaneous Abortion in Dr. Soetomo General Hospital Surabaya : a Case-control Study . 7:1. doi: 10.21070/midwiferia.v7i1.1125

vi Maria T.S.O, Caline N.T.O,Lucas M.M., Cláudio L.S., Márcio V.O.Factors associated with spontaneous abortion: a systematic review. Rev. Bras. Saude Mater. Infant. 20 (2) • Apr-Jun 2020 https://doi.org/10.1590/1806-93042020000200003

vii Sacinti, K.G., Kalafat, E., Sukur, Y.E. and Koc, A., Increased incidence of first-trimester miscarriage during the COVID-19 pandemic. Ultrasound Obstet Gynecol, 57: 1013-1014. https://doi.org/10.1002/uog.23655

viii Neerujah B., Melanie C.D, Jennifer A.H, Judith M.S, Anna L.D. et. al, SARS-CoV-2 infection in the first trimester and the risk of early miscarriage: a UK population-based prospective cohort study of 3041 pregnancies conceived during the pandemic, *Human Reproduction*, Volume 37, Issue 6, June 2022, Pages 1126–1133, https://doi.org/10.1093/humrep/deac062

ix Magnus MC, Gjessing HK, Eide HN, Wilcox AJ, Fell DB, Håberg SE. Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage. N Engl J Med. 2021 Nov 18;385(21):2008-2010. doi: 10.1056/NEJMc2114466. Epub 2021 Oct 20. PMID: 34670062; PMCID: PMC8552533.

[x] Naing L, Nordin R, Rahman HA, Naing YT. Sample size calculation for prevalence studies using Scalex and ScalaR calculators. BMC Medical Research Methodology, 22(1), 1-8 2022.