

**PREVALENCE AND ASSOCIATED FACTORS OF
URINARY TRACT ANOMALIES IN CONGENITAL
HEART DISEASE**

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CHAPTER I: PRELIMINARIES

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ABBREVIATIONS

ASD	Atrial septal defect
AVSD	Atrio-ventricular septal defect
CHD	Congenital heart disease
CoA	Coarctation of aorta
HUSM	Hospital Universiti Sains Malaysia
IQR	Interquartile ranges
LPA	Left pulmonary artery
MAPCAs	Major aortopulmonary collateral arteries
PA	Pulmonary atresia
PDA	Patent ductus arteriosus
PS	Pulmonary stenosis
RPA	Right pulmonary artery
SD	Standard deviation
TA	Truncus arteriosus
TGA	Transposition of great arteries
TOF	Tetralogy of fallot
UTA	Urinary tract anomaly
VSD	Ventricular septal defect

ABSTRAK

Urografi yang dilakukan selepas angiokardiografi adalah merupakan prosedur rutin di sesetengah tempat. Ianya dilakukan berdasarkan konsep penggunaan media kontras semasa prosedur tersebut yang mana akan disingkirkan oleh sistem urinari. Ini membolehkan saluran kencing/urinari ini dapat dilihat. Tujuan kajian ini dilakukan adalah untuk menentukan prevalens ketidaknormalan saluran kencing di kalangan pesakit jantung kongenita dan juga untuk mengetahui faktor-faktor berkaitan yang menyumbang kepada berlakunya ketidaknormalan ini di kalangan pesakit tersebut. Kajian penilaian rekod secara retrospektif ini melibatkan penilaian imej-imej urografi yang diambil selepas angiokardiografi, dalam tempoh 5 tahun. Sebanyak 244 pesakit terlibat dalam kajian ini. Faktor-faktor yang dikaji adalah jantina, umur ibu pesakit ketika pesakit dilahirkan, kewujudan sindrom atau ketidaknormalan kongenita selain struktur jantung, bilangan struktur jantung yang tidak normal pada seseorang pesakit dan juga jenis penyakit jantung yang dialami (*acyanotic* atau *cyanotic*). Regresi logistik pelbagai digunakan untuk mengenalpasti faktor-faktor bebas yang berkaitan dengan ketidaknormalan saluran kencing di kalangan pesakit jantung kongenita. Didapati bahawa prevalens ketidaknormalan saluran kencing adalah 15.6%, manakala jenis penyakit jantung *cyanotic* adalah satu-satunya faktor untuk menjangka terjadinya ketidaknormalan saluran kencing di kalangan pesakit jantung kongenita (*OR* yang diubahsuai 2.2, 95% CI 1.06, 4.63). Kesimpulannya, prevalens ketidaknormalan saluran kencing di kalangan pesakit jantung kongenita di dalam kajian ini adalah setanding dengan kajian-kajian lain. Prevalens yang tinggi ini menjadikan ujian

saringan secara rutin amatlah diperlukan untuk mengenalpasti kewujudan saluran kencing yang tidak normal di kalangan pesakit jantung kongenita terutamanya yang menghadapi pesakit jantung jenis *cyanotic*.

Kata-kata kunci : Penyakit jantung kongenita; Ketidaknormalan salur kencing; Urogram selepas angiokardiografi

ABSTRACT

Urography following an angiocardiography has become a routine procedure in some centres. This has been done on the basis of the usage of contrast media during the procedure that are eliminated via the urinary system which makes the visualization of the urinary tract possible. The purpose of this study is to determine the prevalence of urinary tract anomaly (UTA) in patients with congenital heart disease (CHD) and the associated factors that contribute to the occurrence of UTA in these patients. This retrospective record review involved assessment of post angiocardiography urography images of CHD patients over a five-year period. A total of 244 patients were included in this study. Gender, maternal age at delivery, presence of associated syndrome or other extra-cardiac congenital anomaly, number of heart lesions, and type of CHD (acyanotic or cyanotic) were the factors studied. Multiple logistic regression is used to identify the independent factors associated with UTA in patients with CHD. The prevalence of UTA was 15.6%, whereby cyanotic CHD is the only predicted factor for the presence of UTA in CHD patient (adjusted OR 2.2, 95% CI 1.06, 4.63). As conclusion, the prevalence of UTA in CHD patients in this study is comparable to other studies. This high prevalence warrants a routine screening for UTA in CHD patients especially those with cyanotic type of CHD.

Keywords: Congenital heart disease; Urinary tract anomaly, Post-angiocardiographic urogram

CHAPTER II:

TEXT

SECTION A:

INTRODUCTION

INTRODUCTION

In general, the prevalence of congenital heart disease (CHD) varies between 4 and 10 per 1000 live births (1, 2). More recent studies showed an increasing number of CHD up to 11.89 per 1000 population (3). There are few studies describing about CHD either as an isolated lesion, or in association with extracardiac congenital anomalies, including urinary tract anomaly (UTA) (2, 4-9). Congenital anomalies of the heart and urinary tract are known to occur in a patient in syndromic or non-syndromic patterns. However, so far there is no study describing the associated factors contributing to the findings.

Some patients with CHD need to undergo angiocardiography, a radiographic visualization of the heart and the blood vessels using the injection of a radio-opaque substance. In certain centers, including Hospital Universiti Sains Malaysia, it is a common practice to do post angiocardiographic roentgenogram of the abdomen to visualize the upper part of urinary system especially the kidneys. From this procedure, previous studies showed a number of patients 'accidentally' found to have abnormality of the urinary tract such as duplex kidney/system, hydroureter and hydronephrosis (4-11).

Embryologically, both urinary tract and the heart are originated from the mesoderm, which probably explains this condition. The intermediate mesoderm differentiates into the urogenital structures, whereas the cardiovascular system is originated from the lateral plate mesoderm (12).

However, it is not a routine to screen all patients with congenital heart disease for urinary tract anomaly by any laboratory test or radiological imaging. Since there is possibility of significant association between these 2 major systems involvement, it is worth to study the correlation between these two.

Therefore, we carried out this study to assess the prevalence of UTA and identify the associated factors that increase the likelihood of having UTA in patients with CHD.

SECTION B:

STUDY PROTOCOL

**(i) Document submitted for
ethical approval**

PRINCIPAL INVESTIGATOR : DR ROZIANA ISMAIL (MMED
PAEDIATRIC)
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**URINARY TRACT ANOMALY IN PATIENTS WITH CONGENITAL HEART
DISEASE IN HOSPITAL UNIVERSITI SAINS MALAYSIA**

INTRODUCTION

Some patients with congenital heart disease need to undergo angiocardiology, a radiographic visualization of the heart and the blood vessels using the injection of a radio-opaque substance. In certain centers, including Hospital Universiti Sains Malaysia, it is routine to do post angiocardiology 'kidney shot' also known as roentgenogram of the abdomen to visualize the urinary system especially the kidneys. Some of the patient found to have abnormality of the urinary tract, e.g: duplex kidney, hydronephrosis, single kidney/ agenesis of 1 side of kidney following this procedure. Embryologically, both urinary tract and heart is originated from mesoderm, which probably explains this finding.

Few studies found that there is significant incidence of urinary tract anomaly (UTA) in patients who has congenital heart disease (CHD), and vice versa;

- Incidence of congenital heart disease in normal population is about 0.8% (8/1000), while in patient with underlying UTA, the incidence is about 8% (Ali Mehrizi, The Journal of Paediatric, 2005)
- Incidence of urinary tract anomaly in normal population is 1/600 (0.1-0.2%), whereby in patient with CHD, it is found to be around 7.5-12% (Ali Mehrizi, The Journal of Paediatric, 2005)
- From 260 patient with CHD underwent angiography, 7.7% found to have UTA (Sudhakor R. et al, 1975)
- Autopsy report showed 29% of babies who is known to have CHD also has urinary tract anomaly (Sudhakor R. et al, 1975).

PROBLEM STATEMENT

It is known that certain types of congenital malformations tend to coexist in the same patient. It would be of interest to know whether there is a tendency for cardiac and renal anomalies to develop together. Studies as mentioned above found that certain proportion of patient with congenital heart disease also having abnormality of the urinary tract. However, it is not a routine to screen all patients with congenital heart disease for urinary tract anomaly by any laboratory test or radiological imaging. Since there is possibility of significant association between these 2 major systems involvement, it is worth to study the correlation between these two.

Apart from that, this study also intending to find out whether there is any associated factors that may increase the likelihood of having these 2 major systems involvement of birth defect in a patient.

RATIONALE AND ULTIMATE AIM OF THE STUDY (THE NECESSITY)

1. To justify the importance of post-angiocardigraphic abdominal radiography/ 'kidney shot' as a screening tool to identify any urinary tract anomaly in patient underwent angiocardigraphy.
 - Some patient may need further follow up/ work up as necessary, related to the underlying urinary tract problem
 - E.g: obstructive features- hydronephrosis
 - Some precaution can be taken for example in a patient with single kidney, they might need to be aware of that and prevent any injury or avoid from taking food, substance or medication that can be harmful to the kidney.
 - Early detection of treatable/ potentially significant urinary tract anomaly
e.g: hydronephrosis/ hydroureter
2. To identify significant associated factors that contributes to the likelihood of having urinary tract anomaly in patient with congenital heart disease. This is to consider for regular screening of urinary tract anomaly in this patient in future.
3. No published local data at present

LITERATURE REVIEW

STUDY	PARTICIPANTS	OUTCOME	NECESSITY
<p>Sudhakar R. et al, 1975: <i>Silent Anomalies of the Urinary Tract and Congenital Heart Disease</i></p> <p>Methodology: Observational study</p>	<p>Infants and children with congenital heart disease who underwent angiocardiography/ cardiac diagnostic study in the Paediatric Cardiology Division of The New York Hospital</p>	<p>20 out of 260 patients (7.7%) had a detectable urinary tract anomaly on screening. 8 of these had postmortem confirmation. An additional 21 patients, who underwent cardiac catheterization but not screened for urologic anomalies, were studied at autopsy, in which, 6 of them had a urologic abnormalities (29%)</p>	<p>To determine the incidence and variety of anomalies of the urinary tract</p>
<p>Ali M. 1962: <i>Congenital</i></p>	<p>Autopsy report review- 279 cases</p>	<p>65 of these cases (23%) has</p>	<p>To study the incidence of the</p>

<p><i>Malformation of the Heart Associated with Congenital Anomalies of the Urinary Tract</i> (The Journal of Paediatrics)</p> <p>Methodology: Retrospective, observational study</p>	<p>of having major anomalies of the urinary tract</p>	<p>associated cardiac malformations. 28 of them was an isolated ventricular septal defect.</p>	<p>combination of urinary anomalies with congenital heart disease.</p> <ol style="list-style-type: none"> 1. General incidence 2. Whether this combination occurs more frequently in any specific type of congenital heart disease in the cyanotic or acyanotic patient 3. Whether such malformations of the urinary system are associated
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			with an increased frequency of pulmonary hypertension
<p>A. Humphry and J.D. Munn, Canad. Med. Ass. Journal 1966, vol. 95</p> <p>Methodology: Observational study</p>	<p>450 patients who had angiocardiology done with a posterior roentgenogram of the abdomen following the examination.</p>	<p>Out of 450 cases, 421 patients are studied (another 29 cases- excluded from the study). 2% of them (9 out of 421) had serious urinary tract disease. ~3.5% (n= 15) had anomalies which were of no clinical significance.</p> <p>No significant difference was found in the incidence of the studied 4 renal anomalies (i.e:</p>	<p>To determine the types and incidence of abnormalities of the urinary tract in patients undergoing angiocardiology investigation for congenital cardiovascular disease</p> <p>Compare the incidence of four types of renal anomalies in these cardiac patients with the incidence in patients without cardiac disease</p>

		bifid collecting system, rotated kidney, horseshoe kidney and ectopic kidney) in the 2 groups	
B Adhisivam et al, 2005: <i>Cardiovascular Malformations Associated with Urinary Tract Anomalies</i> (Indian Journal of Nephrology) Methodology: Descriptive study	58 children with urinary tract anomaly and clinical suspicion of cardiovascular malformations (CVM), in Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India. Study period: 9 years (1994 to 2002)	34 % of patients (n= 20) had CVM by echocardiography. 28 children has normal finding, and the remaining children (n= 10), echocardiography could not be done (unconsented by parents)	To identify the various cardiovascular malformations that occur in children with urinary tract anomaly
Belinda M. et al, 1990: <i>Sonographic Screening for Renal Tract</i>	109 children with congenital heart disease (CHD) who admitted to the Department of	The incidence of significant urinary tract anomaly in these patients is 11.9% (13 out of	To justify the importance of sonographic screening of the renal tract in

<p><i>Anomalies Associated with Congenital Heart Disease</i></p> <p>Methodology: Observational, prospective study</p>	<p>Paediatrics at the National University Hospital, Singapore, for cardiac catheterization.</p> <p>These patient were subjected to examination of their renal tracts by real-time sonography</p>	<p>109). None of them were symptomatic of the urinary tract.</p> <p>Study also showed that children with associated extracardiac anomalies had a significantly higher incidence of renal tract anomalies (39.1%) compared to those with isolated CHD (4.7%)</p>	<p>patients with congenital heart disease, especially in those with multiple congenital defects</p>
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OBJECTIVES

GENERAL OBJECTIVE

1. To study the prevalence of urinary tract anomaly (UTA) in patient with congenital heart disease

SPECIFIC OBJECTIVES

1. To describe the demographic background of patient underwent angiocardiography at ICL in HUSM
 - a. To determine the following associated factors (gender, maternal age at delivery, presence of associated syndrome or other extracardiac congenital anomaly, number of cardiac lesion i.e: single versus multiple, and type of heart disease i.e: cyanotic versus acyanotic, with the presence of urinary tract anomaly in patient with congenital heart disease.

STUDY HYPOTHESIS

There are significant association between the gender, maternal age, presence of associated syndrome/ other extracardiac congenital anomaly, number of cardiac lesion, and type of heart disease with the presence of urinary tract anomaly in patient with congenital heart disease, underwent angiocardiography in Invasive Cardiac Laboratory in HUSM from year 2010 to 2014.

METHODOLOGY

- Study design and location
 - Retrospective record review, cross sectional study
 - This study will be done in Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan.

- Study population
 - The reference population is the patient with congenital heart disease who underwent angiocardiology at Invasive Cardiac Laboratory (ICL), HUSM

- Sampling frame
 - 1st of January 2010 till 31st of December 2014

INCLUSION CRITERIA

All patients (regardless of age) with underlying congenital heart disease who underwent angiocardiology at ICL, HUSM since 1st of January 2010 till 31st of December 2014.

EXCLUSION CRITERIA

1. Kidney shot not done/ poor quality of radiographic image/ unable to be interpreted
2. Missing medical record

RESEARCH INSTRUMENT/ DATA COLLECTION

- Data will be extracted from ICL reports/notes and medical records

STATISTICAL ANALYSIS

Descriptive statistic

- Continuous variables: will be expressed as mean and standard deviations (if data are normally distributed) or as median and interquartile ranges (if data are not normally distributed)
- Categorical variables: as proportions
- Differences between groups will be evaluated using;
 - Student's t test (comparing normally distributed variables)- continuous variable
 - Chi square : for categorical data
 - Wilcoxon or Mann-Whitney U tests (comparing variables that are not normally distributed)

Associated factors between urinary tract anomaly and the variables of interest

- Simple and multiple logistic regression

SAMPLE SIZE

1. Prevalence of urinary tract anomaly in congenital heart disease

Sample size is calculated using the formula:

$$n = (Z^2 \times P (1 - P)) / e^2$$

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion

e = desired precision (half desired CI width)

For small populations n can be adjusted so that $n(\text{adj}) = (N \times n) / (N + n)$

- Estimated proportion = 9.6% (0.096)
 - Chest, 67: June 1975, *Silent Anomalies of Urinary Tract and Congenital Heart Disease*
- Confidence level = 0.95
- Desired precision of estimate = 0.05
- Population size = 1000

This utility calculates the sample size required to estimate a proportion (prevalence) with a specified level of confidence and precision.

Using the above formula;

$$\text{Sample size, } n = (1.96^2 \times 0.096 (1 - 0.096)) / 0.05^2$$

$$= 134$$

2. Association between urinary tract anomaly in patient with congenital heart disease with the variable of interest

To compute a sample size for a binary logistic regression requires prior knowledge about the model, such as the expected odds ratio (effect size), proportion of observations in either group of the dependent variable, distribution of each independent variable, and degree of relatedness among independent variables. However, for this study, because of the limitation in availability of literature reviews, these figures are not known. Thus, it is best to use a **rule of thumb** to determine an appropriate sample size.

Hosmer, Lemeshow, and Sturdivant (2013) suggest a minimum sample of 10 observations per independent variable in the model, but caution that 20 observations per variable should be sought if possible.

Likewise, Leblanc and Fitzgerald (2000) suggest a minimum of 30 observations per independent variable. Based on these suggestions and what is feasible, a minimum sample size of (#predictors*10) to (#predictors*30) should be sought to achieve empirical validity.

In this study, there are 5 independent variables involves;

- Gender
- Maternal age
- Associated syndrome/ other extracardiac congenital anomaly
- Number of cardiac anomalies
- Type of congenital heart disease (cyanotic vs acyanotic heart disease)

We decided to have 10 observations per variable;

$$\begin{aligned}(\text{Number of variables} + 1) \times 10 &= (5+1) \times 10 \\ &= 60 \text{ samples per arm}\end{aligned}$$

$$\begin{aligned}\text{Thus, sample size} &= 60 \times 2 \\ &= \mathbf{120}\end{aligned}$$

However, the cases in intensive cardiac laboratory (ICL) HUSM per year are estimated around 100- 120 cases per year. This brings a total of about 500 cases which will be reviewed for this study (from year 2010 to 2015) in which more than the calculated sample size is needed. But there will be a number of cases estimated to be dropped out of the study for various reasons such as missing data/information.

SAMPLING METHOD

No sampling method was applied for this study. All patients who underwent angiocardiology at Invasive Cardiac Laboratory, Hospital Universiti Sains Malaysia (HUSM), from year 2010 to 2014 are included in this study.

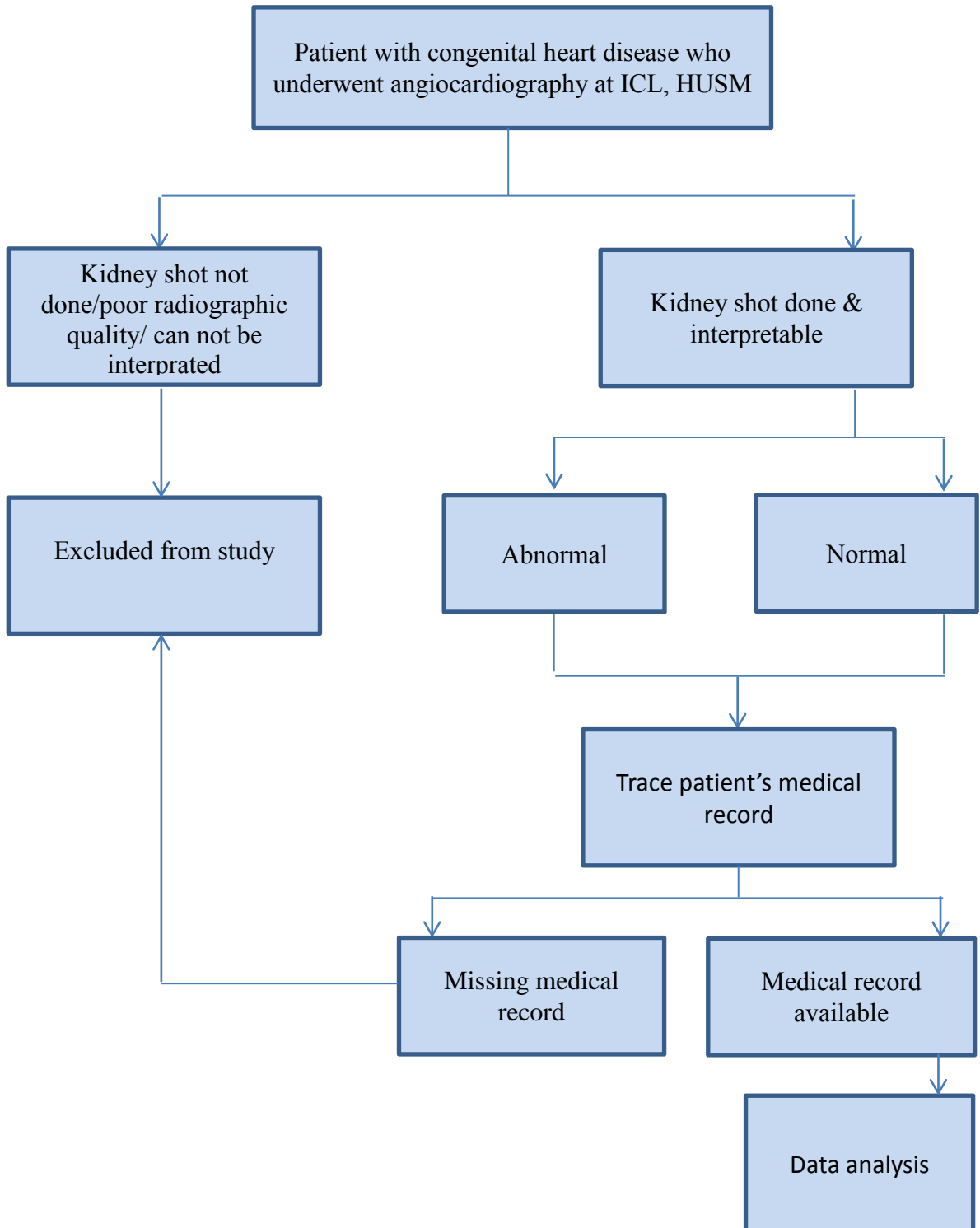
Target population : Patient with congenital heart disease

Source population : Patient with congenital heart disease who underwent angiocardiology at HUSM

Sampling frame : Number of patients during study period (1st of January 2010 till 31st December 2014)

Study sample : Selected participants/ medical records

FLOW CHART



VARIABLES OF INTEREST (INDEPENDENT VARIABLES)

- Gender
- Maternal age
- Associated syndrome/ other extracardiac congenital anomaly
- Number of cardiac anomalies
- Type of congenital heart disease (cyanotic vs acyanotic heart disease)

DEPENDANT DATA

- Urinary tract anomaly (present or absent)

VARIABLES DEFINITION

- Gender
 - Male
 - Female

- Maternal age
 - Young mother : less than 35 years old
 - Advanced maternal age : 35 years old and above

- Associated syndrome/ other extracardiac congenital anomaly
 - Present
 - E.g: Down syndrome or other chromosomal abnormality, congenital anomaly involving other organs such as limb defect/ spina bifida etc
 - Absent
 - Isolated congenital heart defect

- Number of cardiac defect
 - Single
 - Multiple (more than one defect)

- Type of congenital heart disease
 - Cyanotic
 - Acyanotic

EXPECTED RESULT/ DUMMY TABLE

Table 1: Demographic and clinical characteristics of patients underwent angiocardiography in Hospital Universiti Sains Malaysia (HUSM) in year 2010 to 2014

Characteristics	Mean (SD)	n (%)
Age		
Maternal age		

Table 2: Associated factors for the incidence of urinary tract anomaly in patient with congenital heart disease

Characteristics	Crude b (95% CI)	Adjusted b (95% CI)	p-value
Gender			
Male			
Female			
Maternal age			
Young			
Advanced age			
Associated syndrome/ other extracardiac congenital anomaly			

Present

Absent

Number of cardiac defect

Single

Multiple

Type of congenital heart

disease

Cyanotic

Acyanotic

GANTT CHART- as attached

ETHICAL ISSUE

1. Ethical approval will be obtained from Human Research Ethics Committee, HUSM
2. The data will be extracted from the medical records and ICL notes/report which contain the name, identification data and address, but the data will be kept as a code
3. All information obtained from the records will be kept confidential
4. Informed consent is not required

LIMITATION

- Justification of having urinary tract anomaly is based on the finding from the ‘kidney shot’ in which does not resembles the abnormality of the urinary tract (if present) as a whole
- Poor documentation of the finding during the procedure (angiocardiography) as well as in the patient’s medical records in identifying the associated factors contributing to the occurrence of both urinary tract anomaly and congenital anomaly in each study candidate
- Missing data/ records increase the ‘drop out’ case, thus reduce the number of study sample

CONCLUSION

Post-angiocardiographic roentgenogram of the abdomen or ‘kidney shot’ is a simple but yet an important measure to consider in all patients with congenital heart disease who underwent angiocardiography. By identifying the patient who are at risk of having these 2 major systems involvement of congenital birth defects, early detection of urinary tract anomaly may help to prevent the long term complications by early appropriate intervention and management.