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Research Article

Safety and Efficacy Assessment of Intrauterine Contraceptive Devices (IUCDs) in Asian Population: A Systematic Review and Meta-Analysis

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Abstract

Aim: The primary objective of this study is to provide safety data, using the case reports from the Asian population, and understand if co-variables of patients and intrauterine contraceptive devices have any influence on the number of adverse events. The secondary objective is to perform a meta analysis of the prevalent adverse events further to interpret whether there was any significant difference between their occurrences.

Methods: The PubMed database and cochrane library were searched for published case reports and series using the medical subject heading term "Intrauterine Devices/adverse effects". Further seriousness analysis and casualty assessment was also performed. A forest plot was obtained for comparing the two of the most commonly occurring adverse events.

Results: Based on the twenty-six studies included, the majority were in the age group of 25-44 years. The highest number of adverse events was observed with the copper intrauterine contraceptive devices, and the practice of post-partum insertion of intrauterine contraceptive devices affected the number of adverse events. The most common adverse event was migration, followed by the failure of contraception for which a meta-analysis was performed. Results of meta-analysis also favoured migration.

Conclusions: This systematic review analysed the intrauterine contraceptive devices related adverse events, creating a knowledge base for sensitizing the healthcare workers.

Keywords: Adverse Events; Intrauterine Contraceptive Device (IUCD); Contraception; Public Health; Asian Population

Introduction

Contraceptive options are of several types, namely reversible methods of birth control, hormonal types, barrier methods, fertility awareness, lactational amenorrhea, emergency contraception, and permanent sterilization [1]. Long-acting reversible contraceptives (LARC) such as intrauterine contraceptive devices (IUCDs) are hassle-free and low-cost methods for preventing unwanted pregnancy [2]. The market size of IUCDs is estimated to grow upto USD 500.4 million by 2025 [3]. Countries like India, Nigeria, Madagascar, etc., have ensured the availability of IUCDs at the primary health care centres on a no-cost basis [4]. Primarily, two types of IUCDs are commercially available-hormonal and copper type [5]. where the former acts by suppressing ovulation and the latter acts by releasing copper ions into the uterus producing a spermicidal action [6].

The use of IUCDs are associated with adverse events that include but are not limited to, bleeding, uterine perforation, and bowel perforation [7]. IUCD has been recognized as a medical device due to its highly invasive nature and often undergoes stringent regulations [8,9]. Despite the readiness of the regulatory framework, there are starting gaps regarding the collection, assimilation, analysis, and publishing of relevant and reliable safety data. The pharmacovigilance database-"Vigiaccess" identifies the drug or drug and device combinations, but not 'copper IUCDs'. The majority of the reported adverse events (84,719) in Vigiaccess under the category of the reproductive system and breast disorders belonged to Mirena/Emily (hormonal birth control devices). Shockingly, Asia accounts for only 4% of these reports [10].

In general, an adverse event can be either serious or non-serious [11]. Any event is marked serious if it causes death, life-threatening situation, patient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect, requires intervention to prevent permanent impairment or damage, or leads to jeopardization of the patient. Events that may require medical or surgical intervention (treatment) to prevent one of the other outcomes are also categorized as serious [11].

In the 1950s, an American model of IUD, named 'Dalkon shield' was reported to induce 'pelvic inflammatory disease' [12]. This led to a revolutionary move in the United States-Food and Drug Administration (US-FDA) i.e. the introduction of the 'Medical Device Amendment' in the year 1976 [13]. To bridge the existing lacuna, this systematic review attempts to analyze the adverse events related to the use of IUCDs, create a knowledge base that can sensitize the users and healthcare workers.

The primary objective of this study is to provide safety data, using the case reports from the Asian population available on the most common database i.e. PubMed, while observing and classifying the adverse event that occurred in large numbers. Furthermore, an attempt is also made to investigate if the co-variables of the patients and IUCD have any influence on the number of the associated adverse events. The secondary objective is to perform a meta-analysis of the prevalent adverse events and to interpret the statistical or quantitative significant difference between their occurrences.

Materials and Methods

The systematic review was performed according to the PRISMA guidelines (Appendix-I). As the study primarily focuses on the Asian region, reports from Asian countries were included. Further, data was screened and then compiled based on decided population, intervention, comparator, and outcome (PICO) parameters. The following PICO parameter was framed for this systematic review (Table 1). Commonly occurring adverse events and their association with co-factors of patients and IUCD were studied. Additionally, a meta-analysis was performed to evaluate the occurrence of the two of the most frequently observed adverse event.

Table 1: The Population, Intervention, Comparators and Outcomes (PICO), parameter designed for the study

Population	**Gender: FEMALE** **Age Group: >18 years** **Intervention: IUCD†** **Reason for intervention: CONTRACEPTION** **Race/Ethnicity: ASIAN**
Intervention	IUCD†
Comparators	NIL
Outcomes	Adverse Events (major and minor)
Type of studies included	Case Reports, Case Series

Search methods for identification of studies

The study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1) [14]. The search was carried out using the 'PubMed' database. 'Intrauterine Devices/adverse effects' was used as the 'Medical Subject Heading (MeSH)' term, alongside filter for the period between '2015-2020', and an additional filter 'case study' through 9, February 2021. In addition, the Cochrane library was also searched using the keyword 'intrauterine contraceptive device adverse event'. However, no such case study was obtained. The ninety-five cases thus obtained were further manually searched and screened according to the decided inclusion criteria. A PRISMA flow chart depicting the screening is shown in figure 1 [14].

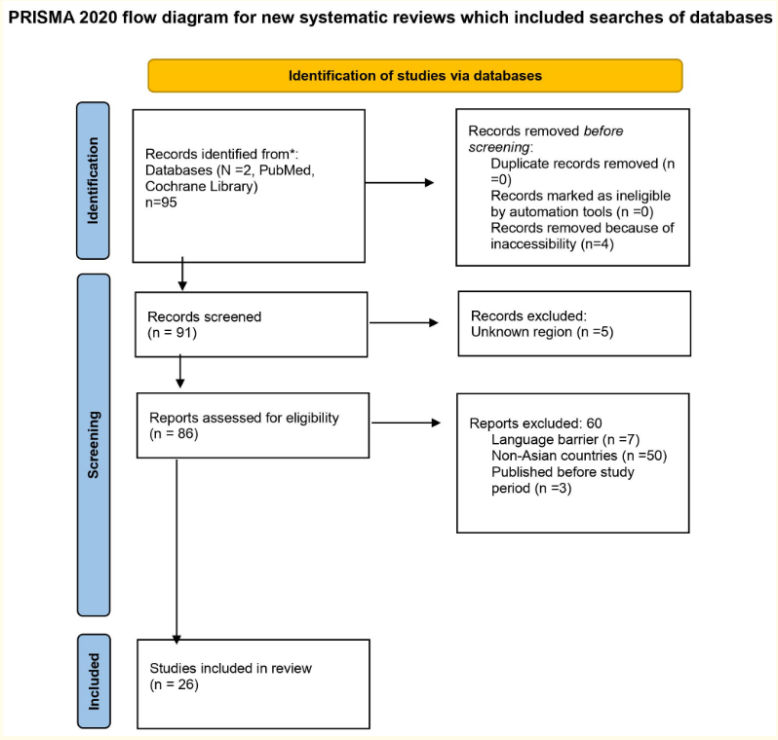

Figure 1: PRISMA flow chart depicting the screening.

Search methods for identification of studies

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Data collection and analysis

Study selection and screening

Inclusion criteria

Articles were included based on accessibility, availability in the English language, origin from the Asian region, and case reports published between 2015-2020. Further, studies were screened manually according to the PICO parameters defined in table 1.

Exclusion criteria

Inaccessible case reports, reports from the unknown or unspecified region, case reports in other languages, studies from non-Asian countries and, cases reported before or after the period taken in inclusion criteria, were excluded.

Data extraction and management

The abstract and full text of twenty-six articles were further screened according to the predefined PICO parameter (Figure 1). Two case reports out of it only had abstractly available [15,16]. To avoid selection bias and any error, the process was run through one more reviewer. We recorded, wherever available, case report origin site, adverse event-related details [adverse event (AE), type of IUCD inserted, reporting year, IUCD implantation year, the reason for the absence of follow up], demographic details of the patient, and patient history [the age of the patient, parity, number of abortions if

any, co-morbidities, if the patient had post-partum insertion and other relevant histories]. Meta-analysis was followed using this data.

Assessment of risk of bias in included studies

The first and foremost bias that was assessed was the reporting of rare and atypical adverse events, which might lead to diversion from common adverse events among the population [17-24]. Often case reports and series are reported after the particular event has happened, i.e. in retrospective manner [25]. This might lead to observation bias and alter the quality and interpretation of the same. Another reason for inherent bias in these reports is that the falsification criterion of science is not tested. Case reports neither can be repeated nor can studies be designed in another similar setup. Often case reports that are similar in observation are included in one case series and are more credible than single reports [26].

Data synthesis

Various comparisons were generated between the occurrence of adverse events and other factors vs. the number of case reports: reporting country, age group classification (based on UN classification) [27], post-partum insertion, parity, and abortion, type of IUCD, comorbidities, years ago IUCD was implanted and common adverse events. In an attempt to establish a relationship between post-partum insertion and the number of cases, tabular data was designed between three parameters, namely 'yes' if it was a post-partum insertion, 'no' if it was not a post-partum insertion, and 'not mentioned' for the case reports that did not have the data required.

Statistical tools and methods

Further through evaluation of the above data, two common adverse events were considered for meta-analysis. The meta-analysis was performed in the Review Manager (RevMan) Version 5.4. The Cochrane Collaboration, 2020 [28]. Using dichotomous outcome, a comparison between the event 'migrations of IUCD' observed and 'failure of contraception' was made. At first, all studies were included and an overall confidence interval, odd ratio, and heterogeneity was studied. Further, those studies with non-estimable data were excluded and thus, a forest plot with the specific odds ratio, confidence interval, and heterogeneity assessors was obtained. Assessment of heterogeneity was performed in the software itself due to

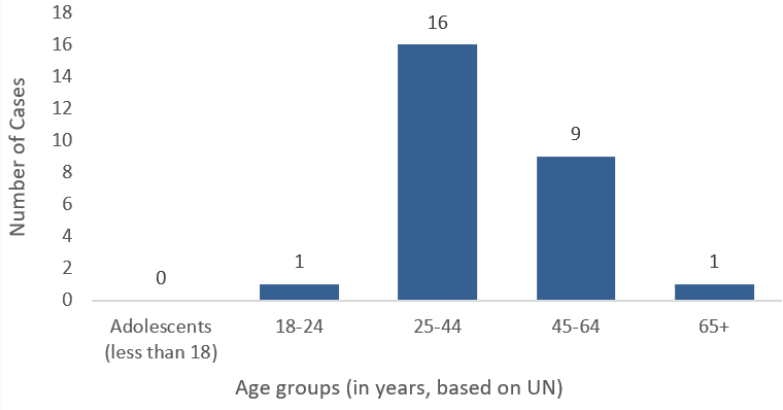

Figure 2: Age group classification of the subjects vs. the cases.

the presence of slight clinical heterogeneity. Chi-square (χ^2), degree of freedom (df), and quantified inconsistency (I^2) were also included in the observation along with the forest plot.

Results

Result of the search

Out of the ninety five articles, nine were excluded as they were inaccessible and data could not be retrived. From the eighty-six accessible case studies, sixty were removed based on exclusion criteria. Three articles, published before 2015 (based on selected study period) and seven articles, not available in the English language (based on the language barrier) were excluded. Fifty cases not satisfying the regional criteria i.e. data from non-Asian countries were

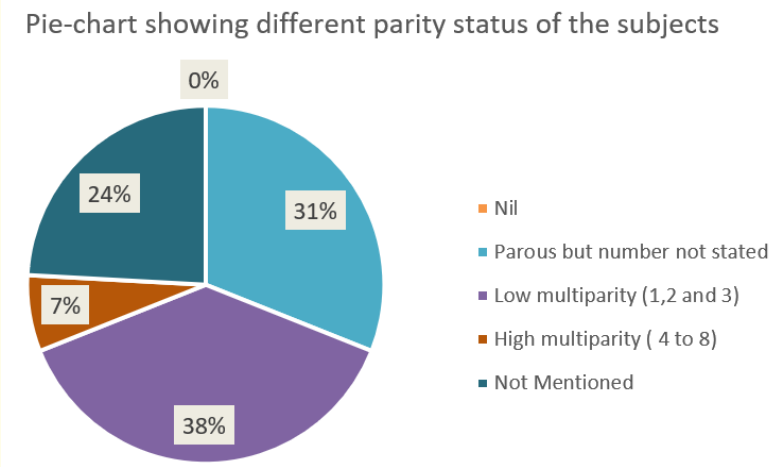

Figure 3: Parity status of the subjects (parous groups vs. number of cases).

also removed. Based on the specified inclusion and exclusion criteria, in total sixty-nine case studies and articles were removed. Finally, twenty-six studies were included in the systematic review. Out of these selected reports, two studies had only abstracts available in the publication, twenty-five were single case reports and one was a case series of four reports, i.e. in total twenty-nine patients were included.

Distribution of studies among Asian countries

The regional distribution of the number of selected studies was studied and observed that China has the highest number of reports i.e. twelve out of twenty-six, followed by India with four cases, then by Iran, Japan, and Pakistan with two cases each. The least were reported from Saudi Arabia and Sri Lanka having one case each. The large population and the one-child policy implemented in China might be the reason for the higher number of reports from it. Out of the forty-eight Asian countries classified by the UN, only seven countries had case reports or series published in the PubMed database as accessed on 9 February 2021 [29,30].

Study population characteristics in included studies

The age group classification was based on the UN's provisional guidelines on standard international age classification [27]. The age group of 25-44 years has the most number of cases, which may

Table 2: Time-difference recorded between insertion and removal due to AE† vs. the number of cases

How many years ago was IUCD‡ implanted?	Number of cases
Less than a year ago	3
Between 1 to 5 years ago	7
Between 6 to 10 years ago	4
Between 11 to 15 years ago	4
Between 16 to 20 years ago	3
Between 21 to 25 years ago	1
Between 26 to 30 years ago	1

†AE- Adverse Event

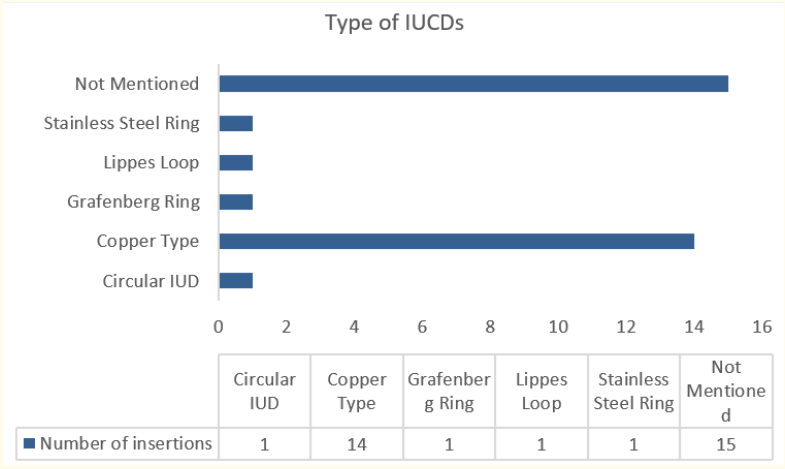

Figure 4: Comparison of the number of cases and IUCD type.

be because itlies in reproducible age and might be having the most insertions for contraception (Figure 2). A relationship between post-partum insertion and the number of cases, could not be established. The reason being fifteen case reports did not have any data about the same [15-18,20-24,31-36]. However, post-partum insertion along with AE was observed in eleven cases [25-26,37-42]. No AE was observed with post-partum insertion in three of them [19,43-44].

Three case reports did not have any co-morbidities associated with them [19,43,44]. Fourteen did not have any data about the same [16-18,20-24,31-33,35,36,39]. Post-partum insertion along with systemic hypertension and controlled diabetes mellitus was observed in a single patient [39]. Endoscopic surgery for gastric polyps, unplanned pregnancy with IUCD in place, and abortion were observed in one patient [35]. All subjects were parous. The majority of the cases belonged to the low-multiparity group comprising the majority. Seven cases did not have any data of parity [15,19-23,36]. Although the data was not complete in all sets, parity seemed to have a relationship with adverse events (Figure 3) [16,31,33,34,38,39,42-44].

A relationship between the number of abortions (both induced and natural) could not be established due to a lack of data and a lesser number of case reports. The majority i.e. 76% of the case reports did not have any data about 'if the subject had an abortion or not' [15-23,25-26,31,34,36,38,41-44]. Only two cases did not

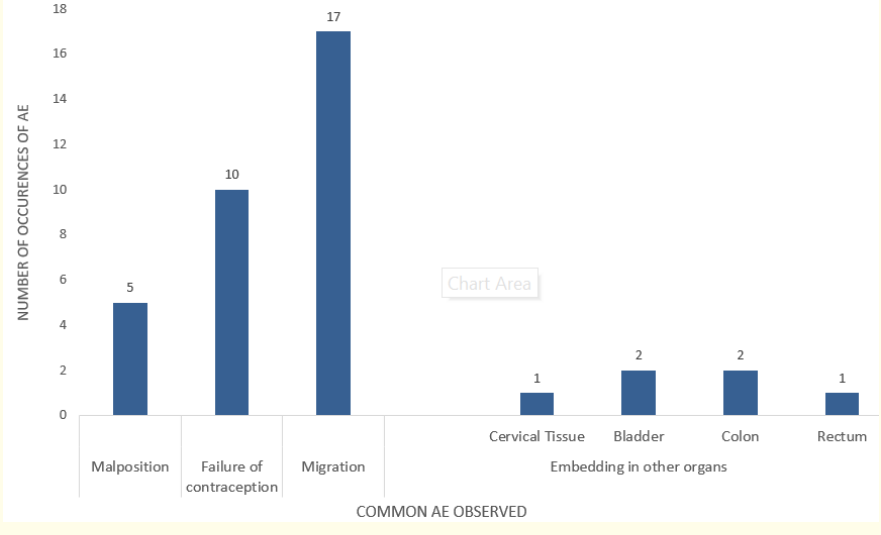

Figure 5: Commonly occurring adverse events (malposition, failure of contraception, migration, and embedding in other organs) with the usage of IUCD.

undergo an abortion [24,37]. One subject had two abortions [33]. About 14% of cases showed single abortion [32,35,39,40].

Type of intrauterine contraceptive device and other IUCD related details

The use of five major types of IUCD was observed in the case reports included in the systematic review. Figure 4 depicts the distribution of the IUCD types, namely circular IUCD [31]. copper type, Grafenberg Ring [33]. Lippes loop [17]. and stainless steel ring [18]. Whether the circular type of IUCD was of stainless steel, polyethylene type or other material was unclear. 48% of the studies involved copper type [16,24-26,31,35-38,40,41,43,44]. indicating an association of copper type IUCD with adverse events. Other than copper type, the rest were each a single case. In around fifteen insertions, the type of IUCD was unknown [15,19-23,26,32,34,35,37,39,42].

Data was combined on whether a follow-up after IUCD insertion occurred or not and what was the reason for the lack of the same. Only four insertions showed that the patient either had a follow-up or faced IUCD related adverse events within a few days or months of insertion [15,23,35,36]. In eight of the insertions, patients were subsequently lost to follow-up due to either their absence during follow-up periods or unknown reasons [18,25,33,34,38,41-43]. The assumption by medical professionals on the spontaneous self-expulsion of the IUCDs was a common reason for the absence of follow-up in six cases [16,17,31,33,40,42]. Time difference of 1-5

Table: Summary of causality assessment and seriousness analysis performed.

The following table gives the summary of causality assessment and seriousness analysis performed:

Study	Adverse Event Short Description	Causal Relationship of AE† with IUCD‡	Serious Adverse Event (Yes, No or could not be established)	If Yes, Reason for marking it as serious
Basiri., *et al*. 2019 [16]	Failure of contraception, Migration	Yes	Yes	Required intervention
Bolat., *et al*. 2019 [42]	Migration, bladder stone, intra-vesical IUD§	Yes	Yes	Required Intervention, Required inpatient hospitalization or prolongation of existing hospitalization.
Chai., *et al*. 2017 [44]	Migration (transmigration), Failure of contraception	Yes	Yes	Required intervention
Chandrasekar., *et al*. 2016 [38]	Migration, Transmural embedding rectum	Yes	Yes	Required intervention
Davoodabadi., *et al*. 2015 [36]	Uterine perforation, Perforation, Migration, Embedding sigmoidal colon	Yes	Yes	Required inpatient hospitalization or prolongation of existing hospitalization
De Silva., *et al*. 2017 [43]	Migration, Large intravesical Bladder stone, intravesical IUCD‡	Yes	Yes	Required intervention
Gul., *et al*. 2019 [21]	Retained IUD§	Yes	Yes	Required intervention (surgery and medical), Required inpatient hospitalization or prolongation of existing hospitalization
Han., *et al*. 2020 [24]	Pelvic Actinomycosis	Possible	Yes	Required intervention (surgical and medical)
Huang., *et al*. 2019 [41]	Migration, sigmoidal perforation	Yes	Yes	Required intervention and required inpatient hospitalization or prolongation of existing hospitalization (22 days)
Jin., *et al*. 2016 [31]	Failure of contraception, Migration, Embedding in bladder	Yes	Yes	Required inpatient hospitalization or prolongation of existing hospitalization (7 days of hospitalization)
Kaleem., *et al*. 2018 [25]	Migration (transmigration) and embedding in sigmoid colon	Yes	Yes	Required intervention and required inpatient hospitalization or prolongation of existing hospitalization (4 days)

Kumar., *et al*. 2016 [37]	Failure of contraception, Migration outside uterus, embedded in bladder	Yes	Yes	Required Intervention
Li., *et al*. 2019 [34]	Failure of contraception, Migration, hydronephrosis, renal failure	Yes	Yes	Required intervention
Lin., *et al*. 2017 [20]	Malposition	Yes	Yes	Required inpatient hospitalization or prolongation of existing hospitalization (probably a month long) or required intervention
Lo., *et al*. 2018 [32]	Failure of contraception, Retained IUD§	Yes	Yes	Required inpatient hospitalization or prolongation of existing hospitalization (2 days)
Magu-dapathi., *et al*. 2015 [17]	Migration, perforation and vesicocervical fistula	Yes	Yes	Required inpatient hospitalization or prolongation of existing hospitalization (7 days of hospitalization)
Mal., *et al*. 2017 [19]	Pelvic abscess caused by a slow growing anaerobic bacterium, Eggerthellalenta	Yes	Yes	Required intervention
Nigam., *et al*. 2015 [26] Case 1, Case 2 and Case 3	Malposition	Yes	Yes	Required intervention
Nigam., *et al*. 2015 [26] Case 4	Malposition, Embedding in cervical tissue	Yes	Yes	Required intervention
Niu., *et al*. 2018 [40]	Failure of contraception, migration and perforation of uterus and bladder	Yes	Yes	Required Intervention
Sahaf., *et al*. 2019 [35]	Failure of contraception, Migration, perforation of rectum	Yes	Yes	Required intervention and required hospitalization or prolongation of existing hospitalization
Shimazu., *et al*. 2017 [18]	Primary uterine diffuse large Bcell lymphoma (DLBCL)	Yes	Yes	Life threatening, Required inpatient hospitalization or prolongation of existing hospitalization
Taira., *et al*. 2019 [22]	Tube-ovarian abscess caused by Rothiaaeria	Possible	Yes	Required intervention and inpatient hospitalization
Yamamoto., *et al*. 2019 [23]	Fusobacterium necrophorum septic pelvic thrombophlebitis	Yes	Yes	Life threatening, Required intervention (treatment)
Ye., *et al*. 2018 [33]	Failure of contraception, migration, embedding in rectum	Yes	Yes	Required Intervention
Zhang., *et al*. 2019 [31]	Intravesical Migrated Intrauterine Device in Bladder	Yes	Yes	Required intervention
Zhou., *et al*. 2018 [39]	Failure of contraception, Migration, Sigmoid colon inflammation	Yes	Yes	Required Intervention, Required inpatient hospitalization or prolongation of existing hospitalization (5 days)

Appendix III: Statistical data obtained for meta-analysis including all the studies.

A tabular form of the statistical data obtained for meta-analysis including all the studies of this systematic review.

Study	Migration	Total AE	Failure of contraception	Total AE	Weight	Odds Ratio (non-event) [Fixed, 95% Cl]
Davoodabadi., *et al*. 2015 [36]	1	4	0	4	5.80%	0.26 [0.01, 8.52]
Magudapathi., *et al*. 2015 [17]	1	3	0	3	5.50%	0.24 [0.01, 8.62]
Nigam., *et al*. 2015 [26]	0	5	0	5	NIL	Not estimable
Chandrasekar., *et al*. 2016 [38]	1	2	0	2	4.90%	0.20 [0.00, 8.82]
Jin., *et al*. 2016 [31]	1	3	1	3	6.10%	1.00 [0.03, 29.81]
Kumar., *et al*. 2016 [37]	1	3	1	3	6.10%	1.00 [0.03, 29.81]
Chai., *et al*. 2017 [44]	1	2	1	2	4.60%	1.00 [0.02, 50.40]
De Silva., *et al*. 2017 [43]	1	3	0	3	5.50%	0.24 [0.01, 8.62]
Lin., *et al*. 2017 [20]	0	1	0	1	NIL	Not estimable
Mal., *et al*. 2017 [19]	0	1	0	1	NIL	Not estimable
Shimazu., *et al*. 2017 [18]	0	1	0	1	NIL	Not estimable
Kaleem., *et al*. 2018 [25]	1	2	0	2	4.90%	0.20 [0.00, 8.82]
Lo., *et al*. 2018 [13]	0	2	1	2	4.90%	5.00 [0.11, 220.62]
Niu., *et al*. 2018 [40]	1	4	1	4	6.90%	1.00 [0.04, 24.55]
Ye., *et al*. 2018 [33]	1	3	1	3	6.10%	1.00 [0.03, 29.81]
Zhou., *et al*. 2018 [39]	1	3	1	3	6.10%	1.00 [0.03, 29.81]
Gul., *et al*. 2019 [21]	0	1	0	1	NIL	Not estimable
Huang., *et al*. 2019 [41]	1	2	0	2	4.90%	0.20 [0.00, 8.82]
Li., *et al*. 2019 [34]	1	4	1	4	6.90%	1.00 [0.04, 24.55]
Sahaf., *et al*. 2019 [35]	1	3	1	3	6.00%	1.00 [0.03, 29.81]
Taira., *et al*. 2019 [22]	0	1	0	1	NIL	Not estimable
Yamamoto., *et al*. 2019 [23]	0	1	0	1	NIL	Not estimable
Zhang., *et al*. 2019 [24]	1	2	0	2	4.90%	0.20 [0.00, 8.82]
Basiri., *et al*. 2019 [16]	1	2	1	2	4.60%	1.00 [0.02, 50.40]
Bolat., *et al*. 2019 [42]	1	3	0	3	5.50%	0.24 [0.01, 8.62]
Han., *et al*. 2020 [24]	0	2	0	2	NIL	Not estimable

years between insertion and removal was recorded in 23% of the subjects. The same was unknown for 20% of insertion (Table 2).

Adverse events and symptoms

The most common adverse event noted was the migration of the IUCD to various organs. Figure 5 shows commonly occurring adverse events (malposition, failure of contraception, migration, and embedding in other organs) with the usage of IUCD. In total sixty-three adverse events were recorded from these reports. Around 45% were noted to be that of migration [16,17,25,31,33,44]. Malposition, identified as tilt or abnormal positioning of IUCD but inside the uterus itself, was observed to be the least common adverse event as it occurred in 11% of the cases [20,26]. Failure of contraception was recorded in 26% of the cases [16,31,35,37,39,40,44]. Migration along with embedding in other organs was recorded in 18% of the cases. The embedding or movement of the device into various other tissues like embedding in the bladder [31,37], rectum [33,38], colon [25,36], and cervical tissue [26]. was observed (Figure 5).

Other adverse events that were recorded were perforation/erosion of uterus [36,40], perforation/erosion of other organs [17,35,36,40,41], retained IUCD [24,32] intravesical IUCD [15,42,43], bladder stone [42,43], renal failure [34], hydronephrosis [34], vesicocervical fistula [17], sigmoidal inflammation [39]. unusual complication of LEEP procedure [24], pelvic actinomycosis [21], primary uterine diffuse large B cell lymphoma (DLBCL) [18], pelvic abscess caused by a slow-growing anaerobic bacterium, *Eggerthellalenta* [19], tube ovarian abscess caused by *Rothiaaeria* [22], and *Fusobacterium necrophorum* septic pelvic thrombophlebitis

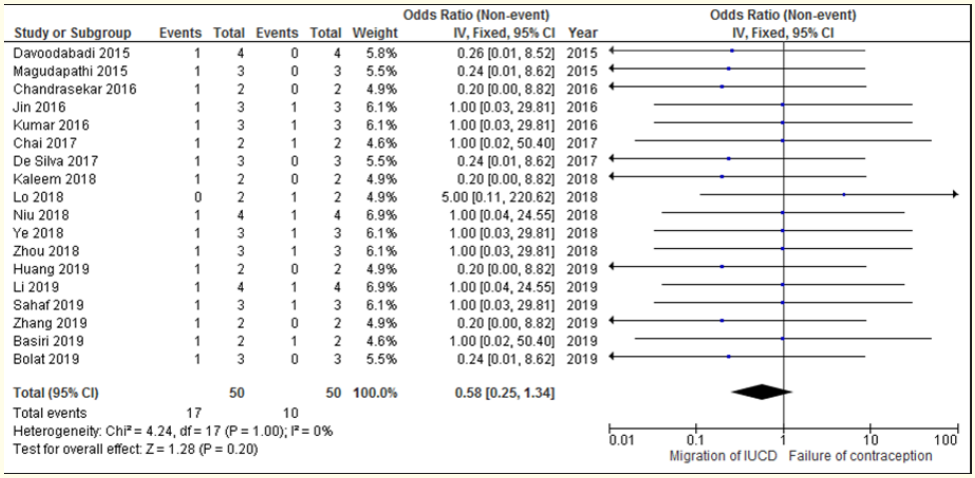

Figure 6: Forest plot of the cases with migration and failure of contraception.

[23].

Seriousness and causality assessment of the case reports

The seriousness of the adverse event was assessed based on the WHO-UMC definition of seriousness [11]. Causality assessments of the case reports were performed to understand whether a causal relationship between the adverse event and IUCD inserted exists or not. On exploration, it was noted that reports, Han et al. [24] and Taira et al. [22] had a "possible" relationship, indicating that the AE might have been caused by the device. However, other causes cannot be ignored. The rest of the studies had a confirmed causal relationship between the AE and IUCD inserted [45,46]. All studies had a serious adverse event, marked by either life-threatening event (2/29 cases), requiring hospitalization or prolongation of existing hospitalization (12/29 cases), or requiring medical and/or surgical intervention (21/29 cases) (table).

Statistical analysis

A meta-analysis was performed to understand whether there was a significant difference in the occurrence of two of the most common adverse event, namely migration of the intrauterine device and failure of the contraception. From the total of sixty-three adverse events, seventeen migration and ten failure of contraception were studied with a confidence interval of 95% in the random effect model, to accommodate the heterogeneity of the studies. The total weight of each study alongside the odds ratio was thus obtained with the exact confidence interval from the software (Appendix-III). Eight studies that did not yield a significant weight to the forest plot [18-24,26]. were removed from the final version of the meta-analysis.

The lower and the upper limit of the confidence interval (CI) for all the studies were 0.25 and 1.34, respectively. An overall odds ratio (OR) of 0.58 was also obtained. The Tau (τ), chi-square (χ^2), and I^2 values were 0.00, 4.24, and 0% at a df of 17 (p value = 1.00), respectively. The I^2 value between 0 to 40% usually denotes a non-significant heterogeneity or the value of difference might not be that important [47]. For the present meta-analysis, with 95% confidence, it may be concluded that neither the χ^2 value was too high nor the p-value was too low to provide any evidence of heterogeneity [47]. For ease of understanding, a forest plot was obtained without the studies (Figure 6) that did not have significant or desirable events (migration or failure in this case). There is no significant difference between the two events (p-value=0.20, Z=1.28) (Figure 6). From the forest plot, it is evident that most of the cases have a higher incidence of migration of the IUCD than the failure of contraception.

Discussion

The overall result of the systematic review and meta-analysis indicates that there is a need for more studies or case reports to analyze the data and come to a definite conclusion. However, the commonly observed adverse events and the comparison between the two of the most frequent one provides the scope for understanding what needs to be counselled to the patients. Most of the follow-ups didn't occur due to either the absence of the patient or was a misdi-

agnosis on the physician's side. With better awareness, the lacuna in missing data and lack of reports can be addressed. The strength of the study lies in its inclusion of all types of intrauterine devices in the review. Since the number of studies included was small, the systematic review was able to include as much data from the case reports as possible. The targeted subjects and study was of Asian origin, and hence, provides information to the healthcare providers of the countries about the need for more robust and elaborate reports that need to be published.

This systematic review has its own bias and limitations. The first and the foremost bias was the inclusion of recent studies and the second, being the inclusion of published case reports and case series alone. No author was contacted for missing data or inaccessibility of studies. Articles in a language other than English were not translated. Two of the case reports did not have complete data [15,16]. and often in many case reports the year of IUCD insertion' [20,21,26,32]. and 'date of reporting' [15-24,26,31-33,35-44]. was missing. Additionally, as observed in Figure 6, there was a wide CI in each of the studies which might indicate a lack of complete evidence to provide a true effect size [48].

Madden et al. concluded that young women between the age-group 14-19 experienced more expulsion/AE compared to older women [49]. However, no such conclusion could be drawn from our age groups. Migration and migration followed by embedding were observed in 45% and 11% of cases, respectively. Boortz et al. concluded on similar grounds by combining a series of case reports, that migration followed by either expulsion, embedding in surrounding organs, and perforation of the uterus is a frequently encountered phenomenon [50]. Abdominal radiography alongside regular follow-up can be useful for detecting a migration or extra-uterine device [50]. Failure of contraception was the second major adverse event occurring in our review (26%). Even though IUCD is known to be quite effective, the failure rate of Cu-T380A IUCDs is around 0.8% (0.1-1.4 per 100 insertions) [51-53]. Aoun et al. study suggests an increase in expulsion with the usage of copper type IUCD in comparison with levonorgestrel type [54]. Perforation and embedding in the colon are more common than in perforation in other organs. In this systematic review, two cases showed colonic embedding. Colon perforation though rare but is still observed in many case reports across the world [55,56]. Perforation of bladder and embedding seemed to occur as much as in the colon in this systematic review.

Due to the small number of subjects and data unavailability, a variety of factors like parity, abortion and co-morbidities could not be assessed for correlation. Post-partum insertion could be a cause for expulsion and migration [57]. However, due to the absence of data, we could not establish a proper statistical link. Post-partum insertion (PPI) is a common practice despite the number of device failures due to its higher cost-benefit ratio and success in preventing unwanted pregnancy [57]. One study in Tanzania suggested that 25 out of 511 women discontinued post-partum inserted IUCD usage due to higher abnormalities in the menstrual cycle [58]. Only seventy-one women discontinued usage with 24% getting it done between a period of 0-24 days since childbirth. However, they have concluded that the Cu-T380A continuation rate after PPI is higher with consideration of both safety and effectiveness [58]. Co-morbidities' association with AE could not be established due to limited data. A single patient had comorbidity of hypertension and diabetes. Ashley Sier's project suggests that IUCD removal is associated with a decreased likelihood of hypertension, etc., and an in-

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PRISMA 2020 Checklist

Appendix I: PRISMA Checklist.

Section and Topic	Item #	Checklist item	
TITLE			
Title	1	Identify the report as a systematic review.	✓
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	✓
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify thedate when each source was last searched or consulted.	✓
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	✓
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each recordand each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collec-tionprocess	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	✓
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in eachstudy were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	✓
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed eachstudy and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	

Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics andcomparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or dataconversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	✓
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	✓
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	✓
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting biasassessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

Section and Topic	Item #	Checklist item	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included inthe review, ideally using a flow diagram.	✓
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	✓
Study characteristics	17	Cite each included study and present its characteristics.	✓
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	✓
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision(e.g. confidence/credible interval), ideally using structured tables or plots.	✓
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	✓
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	✓
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			

Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	✓
	23b	Discuss any limitations of the evidence included in the review.	✓
	23c	Discuss any limitations of the review processes used.	✓
	23d	Discuss implications of the results for practice, policy, and future research.	✓
OTHER INFORMATION			
Registration andprotocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	NIL
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	