INFORMATION BRIEF (RAPID REVIEW)

INJECTABLE PROGESTOGEN FOR CONTRACEPTION

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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Rapid Review
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TITLE: Injectable Progestogen for Contraception

PURPOSE

To provide scientific evidence on the effectiveness, safety, and cost-effectiveness of injectable progestogen for contraception following the request by Family Health Development Division, Ministry of Health Malaysia due to concern on its safety.

BACKGROUND

Injectable contraceptives are available in one-, two-, or three-month intervals, depending on the formulation. As of 2009, eight different formulations existed globally (Table 1). In developing countries, family planning programs typically offer progestin-only injectables like depot medroxyprogesterone acetate (DMPA) or Norethisterone enanthate (NET-EN), and sometimes combined injectables (progestin with estrogen). [1]

Table 1: Injectable Contraceptives — Formulations and Injection Schedules. [1]

Common Trade Names	Formulations	Injection Type and Schedule
Progestin-only injectables		
[redacted]	Depot medroxyprogesterone acetate (DMPA) 150 mg	One **intramuscular** (IM) injection every three months
[redacted]	DMPA 104 mg	One subcutaneous injection every three months
[redacted]®	Norethisterone enanthate (NET-EN) 200 mg	One IM injection every two months
Combined injectables (progestin + estrogen)		
[redacted]®	Medroxyprogesterone acetate 25 mg + Estradiol cypionate 5 mg (MAP/E2C)	One IM injection every month
[redacted]	NET-EN 50 mg + Estradiol valerate 5 mg (NET-EN/E2V)	One IM injection every month
[redacted]	Dihydroxyprogesterone acetophenide 150 mg + Estradiol enanthate 10 mg	One IM injection every month
[redacted]	Dihydroxyprogesterone acetophenide 75 mg + Estradiol enanthate 5 mg	One IM injection every month
[redacted]	17 α-hydroxyprogesterone caproate 250 mg + Estradiol valerate 5 mg	One IM injection every month, except two injections in the first month

Three progestin-only injectable contraceptives are available for pregnancy prevention: depot medroxyprogesterone acetate (DMPA) 150 mg/mL administered intramuscularly (DMPA-IM, marketed as [redacted], a lower-dose subcutaneous formulation of DMPA (DMPA-SC) containing 104 mg/0.65 mL [redacted], and norethisterone enanthate

(NET-EN) 200 mg/mL administered intramuscularly. DMPA-SC is available in [redacted] as [redacted] and in a single-dose prefilled glass syringe as S[redacted]. These injectable methods primarily prevent pregnancy by suppressing ovulation, with additional mechanisms including thickening of cervical mucus and thinning of the endometrium. [2]

The progestin-only injectables, primarily depot medroxyprogesterone acetate (DMPA), is a widely used contraceptive, with a global prevalence of 3.9% among women aged 15 to 49, equating to 74 million users in 2019. It is most commonly used in sub-Saharan Africa and South-Eastern Asia, with prevalence exceeding 20% in countries like Indonesia and South Africa, while its use remains low in Europe at just 0.5%. In Malaysia, hormonal contraceptives, including pills (41.9%) and injectables (20.9%), are preferred over non-hormonal methods like condoms (20.4%) and copper IUDs (14.5%). [3, 21]

Depot Medroxyprogesterone Acetate (DMPA) is a progestin-only, water-based injectable contraceptive effective for three months per dose. It is fully reversible and includes a four-week grace period for reinjection, making it highly user-friendly. Its popularity stems from its low cost, wide availability in branded and generic forms, and global regulatory approval in over 179 countries. For DMPA-IM, it is administered as a 150 mg deep intramuscular injection (deltoid or gluteal muscle) every 3 months (13 weeks). The injection can be given up to two weeks late (15 weeks in total) without requiring additional contraception, but if delayed further, additional contraceptive measures are needed for seven days. For DMPA-SC is administered using a prefilled, single-use syringe injected into the thigh or abdomen. It contains 104 mg of progestin and is given as a subcutaneous injection with same schedule as DMPA-IM. Both DMPA primarily inhibits pituitary gonadotropin secretion, leading to anovulation and reduced estrogen production, thereby preventing pregnancy. [1, 4]

Figure 1: depot medroxyprogesterone acetate [redacted]a). [5]

Norethisterone enanthate (NETE), also known as norethindrone enanthate, is a progestogen-only injectable contraceptive used to prevent pregnancy. Administered via intramuscular injection every two months, it functions by inhibiting ovulation. It is used both as a standalone contraceptive and in combination with estradiol valerate in combined injectable formulations. It has been approved in more than 60 countries, including the United Kingdom and several in Europe, Central America, and Africa, but is not available in the United States. It may be used following childbirth, miscarriage, or abortion, with a typical failure rate of two per one hundred women per year. Common side effects include breast pain, headaches, depression, irregular menstrual periods, and injection site pain. While its use is contraindicated in individuals with liver disease and during pregnancy due to potential birth defects, it is considered safe during

breastfeeding. As a long-acting contraceptive, NETE provides a reliable and discreet birth control option, though it does not offer protection against sexually transmitted infections. It was patented in 1951 and NETE came into medical use in 1957 It is listed in the World Health Organization's List of Essential Medicines. [6]

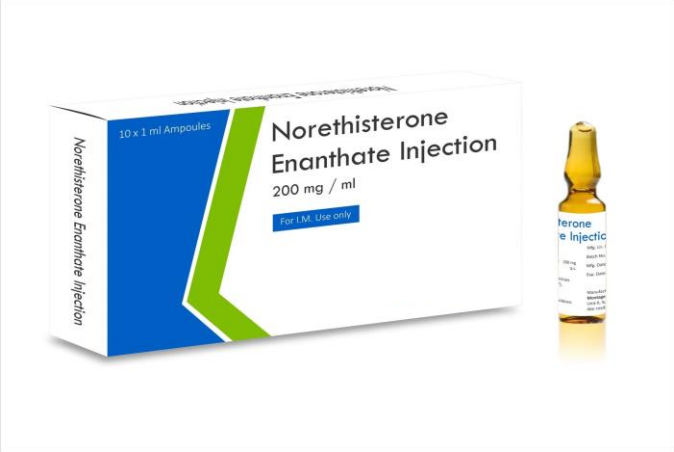

Figure 2: Norethisterone Enanthate Injection. [7]

EVIDENCE SUMMARY

A total of 510 articles were retrieved from scientific databases, including PubMed, the Cochrane Library, and the general search engine Google Scholar, as well as reference lists. The search focused on injectable progesterone for contraception using the keywords: "contraception," "injectable progesterone," "medroxyprogesterone acetate," and "norethisterone enanthate", "meningioma" and "adverse effects". The final search was conducted on 6th March 2025.

Seven studies were included in this review, comprising two systematic reviews, two observational studies, one case report and two cose effectiveness study. Additionally, evidences from the United States Food and Drug Administration (US FDA) website and one safety alert report from the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia, were also included.

SAFETY

Meningioma risk

A case-control study conducted by Roland N et al. (2024) aimed to evaluate the association between progestogen use and the risk of intracranial meningioma and to describe the characteristics of affected women, including age, tumor grade, and anatomical location, while also estimating the number of surgically treated meningiomas attributable to progestogen use. This study included 108,366 women (18,061 cases, 90,305 controls) and utilised data from the French national health database (Système National des Données de Santé, SNDS). Women who underwent surgery for intracranial meningioma between 1st January 2009, and 31st December 2018, were identified as cases, while five matched controls per case were selected based on birth year and geographic region. Pregnant women within two years

before the index date were excluded. Meningioma cases were identified using hospital records with relevant ICD-10 codes (D32, D42, C70) and surgical procedure codes. Progestogen exposure was determined using WHO's Anatomical Therapeutic Chemical (ATC) classification system, considering different administration routes (oral, percutaneous, intravaginal, intramuscular, intrauterine) and specific lookback periods (365 days for systemic progestogens, up to five years for intrauterine systems). Exposure was categorised into three groups: use of the specific progestogen of interest, prior exposure to high-dose progestogens known to increase meningioma risk, and non-exposure. The mean age was 57.6 years. They found most cases occurring at the skull base (55.6%) and the majority classified as benign (92.3%). Mortality was higher among cases compared to controls at two years (2.8% compared to 1.2%) and five years (5.3% compared to 3.4%). No significant association was found for oral/intravaginal progesterone, percutaneous progesterone, dydrogesterone, or spironolactone, while medrogestone (OR 3.49, 95% CI:2.38 to 5.10), **injectable contraceptive medroxyprogesterone acetate (OR 5.55, 95% CI 2.27 to 13.56), and promegestone (OR 2.39, 95% CI:1.85 to 3.09) were linked to increased risk, particularly with prolonged use**. Medrogestone-related meningiomas were often located at the skull base (OR 8.30 for middle base). No malignant tumors were observed among users of these three progestogens. Levonorgestrel intrauterine systems (52 mg and 13.5 mg) showed no significant risk increase (OR 0.94 and 1.39, respectively). The estimated population attributable fractions were 0.17% for medrogestone, 0.04% for medroxyprogesterone acetate, and 0.27% for promegestone, with higher risks observed for chlormadinone acetate (2.58%), nomegestrol acetate (4.08%), and cyproterone acetate (4.68%). [8]

According to the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia, in a safety alert on Progestogens (Cyproterone Acetate, Medroxyprogesterone Acetate, Chlormadinone): Risk of Meningioma (2024) reported that in Malaysia, cyproterone acetate, chlormadinone acetate, and medroxyprogesterone acetate are registered, while nomegestrol, medrogestone, and promegestone are not. Local adverse drug reaction (ADR) reports indicate medroxyprogesterone acetate had the highest reports (239) and adverse events (539) compared to Cyproterone Acetate and Chlormadinone. The adverse events reported were primarily pruritus, rash, and urticaria, with no local cases of meningioma. Healthcare professionals are advised to consider the meningioma risk when prescribing progestogens. Be aware of the potential risk of meningioma with progestogens, especially cyproterone acetate, chlormadinone, and injectable medroxyprogesterone acetate with prolonged use. Avoid high-risk progestogens in patients with a history or presence of meningioma, except in exceptional cases after multidisciplinary evaluation. Use the lowest effective dose for the shortest duration, educate patients on warning symptoms, and monitor high-risk individuals. If meningioma is suspected, consider brain Magnetic Resonance Imaging (MRI) and discontinue treatment if diagnosed and report adverse events to NPRA. Ongoing pharmacovigilance remains crucial to ensure patient safety. This safety alert also highlighted the findings on recent studies and regulatory updates which have confirmed a dose-dependent association between high-dose progestogens and an increased risk of meningioma, particularly with prolonged use. The United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) first identified this risk for cyproterone acetate (⩾ 25 mg/day) in 2020, later extending it to nomegestrol (3.75-5 mg/day) and chlormadinone (5 to10 mg/day) in 2022. In 2023, the French National Agency for the Safety of Medicines and Health Products (ANSM) recommended risk minimisation measures for medrogestone and medroxyprogesterone acetate due to newly identified meningioma risks, similar to those for chlormadinone and

nomegestrol. The ANSM also alerted the European Medicines Agency (EMA), and promegestone marketing in France ceased in 2020. These actions were based on a large French epidemiological study using data from the France National Health Data System (SNDS), published in March 2024 as reported in effectiveness part. [14]

Other risk

A systematic review by Zürcher et al. (2024) was conducted to provide an overview of the existing studies concerning a possible link between progestin-only injectables depot medroxyprogesterone acetate (DMPA) and breast cancer. A comprehensive search across MEDLINE, Embase, Cochrane Library, ClinicalTrials.gov, and ICTRP used a PICO-based strategy. A total of 3,850 records were screened following PRISMA guidelines, with inclusion criteria focusing on women using DMPA and exclusion criteria removing those at high risk for breast cancer or exposed to hormone replacement therapy. After independent screening, ten studies were included in the final review. All included studies were conducted in the United States, Thailand, Mexico, Kenya, Costa Rica, New Zealand, and South Africa, with participant sample sizes ranging from 30 to 4,575 women. Most studies were case–control, except for one pooled analysis and one study comparing observed and expected cancer cases. In this review, seven studies found no overall increased breast cancer risk in DMPA users, with relative risks (RR) ranging from 0.7 to 1.2. However, three studies reported an increased risk, with one study finding an RR of 1.21 (95% CI:0.96 to 1.52), another reporting an odds ratio (OR) of 1.31 (95% CI 1.03 to 1.65), and a third study reporting an RR of 2.6 (95% CI:1.4 to 4.7). The risk appeared to be elevated in current or recent DMPA users, with several studies indicating a higher risk in women younger than 35 years, with RRs up to 2.1 (95% CI:1.1 to 3.8). Some studies suggested that the risk increase was primarily observed in women who had used DMPA for more than 12 months. One study explicitly found no increased risk in current users, reporting an OR of 0.7 (95% CI:0.4 to 1.3). Regarding long-term use, most studies did not indicate a significant increase in breast cancer risk. However, one study found a higher risk for women who had used DMPA for six years or more, with an RR of 3.7 (95% CI 0.63 to 21.5), particularly among those who started using DMPA before age 25 or before their first full-term pregnancy. [3]

Martinez AI et al (2022) reported a case of a 19-year-old female with polycystic ovarian syndrome (PCOS) who developed central diabetes insipidus (DI) after receiving a single injection of depot medroxyprogesterone acetate (DMPA) for contraception and oligomenorrhea. One-month post-injection, she experienced dry mouth, polydipsia, polyuria, and nocturia, which persisted despite multiple courses of antibiotics. Diagnostic tests, including urinalysis, pelvic ultrasound, and thyroid ultrasound, showed no abnormalities. A water deprivation test confirmed central diabetes insipidus (DI), with a serum osmolality of 303 mOsm/kg and urine osmolality of 54 mOsm/kg. The patient's symptoms resolved with desmopressin (DDAVP) treatment, and she continued intranasal vasopressin therapy with sustained symptom relief. [9]

Polis et al. (2016) conducted a systematic review to evaluate the relationship between hormonal contraceptive use and HIV acquisition, particularly focusing on injectable progesterone methods, depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN). A comprehensive literature search was performed through PubMed and Embase. Graphical summaries and meta-analyses were performed to evaluate risk estimates, with a specific focus on DMPA. The study applied a rigorous statistical meta-analysis using a random effects model to estimate the effect of DMPA versus non-use of

hormonal contraception on HIV risk, assessing heterogeneity through the I^2 statistic. This review screened 312 new references, assessed 14 full-text reports, and included ten new studies while excluding four due to irrelevance or duplicate data. A total of 31 studies (34 reports) were analyzed, including a large individual participant data (IPD) meta-analysis that incorporated seven previously unused datasets. The studies primarily focused on hormonal contraceptive use versus non-use (30 studies) and head-to-head comparisons (two studies). Of these, five studies reported a statistically significant increase in HIV risk with DMPA use, with adjusted hazard ratios (adjHR) ranging from 1.45 to 2.04. One study found the largest estimate under a marginal structural model (MSM) at 2.19. Seven studies reported non-significant results, with adjHRs ranging from 0.46 to 1.34. No statistically significant HIV risk increase was found for NET-EN, with estimates ranging from adjHR 0.87 to adjusted incidence rate ratio (adjIRR) 1.76. A meta-analysis of ten estimates from nine studies and unpublished data from an individual participant data (IPD) meta-analysis produced an overall effect estimate of 1.40 (95% CI: 1.23 to 1.59) with an I^2 of 0%. Head-to-head studies showed a statistically significant increased risk of HIV for DMPA versus NET-EN (adjHR: 1.32 to 1.41) and for DMPA versus combined oral contraceptives (COCs) (adjHR: 1.43, 95% CI: 1.23 to 1.67), while NET-EN versus COCs showed a borderline nonsignificant increase (adjHR: 1.30, 95% CI: 0.99 to 1.71). Effect modification analyses indicated higher HIV risk with DMPA among younger women (18 to 24 years old) in one study, while eight studies reported no age-related effect modification. Increased HIV risk was observed in East Africa for COC use (adjHR: 1.58, 95% CI: 1.19 to 2.09) and for DMPA use in East and South Africa (adjHR: 2.09, 95% CI: 1.68 to 2.80; adjHR: 1.30, 95% CI: 1.11 to 1.53), but not in Southern Africa. Additionally, populations engaged in transactional sex work showed an increased HIV risk with COC use (adjHR: 1.51, 95% CI: 1.09 to 2.10). Studies considered at lower risk of methodological bias reported smaller effect sizes for DMPA (adjHR: 1.22, 95% CI: 0.99 to 1.50) and for NET-EN (adjHR: 0.67, 95% CI: 0.47 to 0.96). [11]

The World Health Organization in a guideline entitle of Contraceptive Eligibility for Women at High Risk of HIV (2019) recommend that women at high risk of HIV infection can use all hormonal contraceptive methods and intrauterine devices (IUDs) without restriction as they fall under Category 1 of the Medical Eligibility Criteria (MEC). This includes progestogen-only methods such as progestogen-only pills (POPs), intramuscular depot medroxyprogesterone acetate (DMPA-IM), subcutaneous depot medroxyprogesterone acetate (DMPA-SC), norethisterone enanthate (NET-EN) injectables, levonorgestrel (LNG) implants, and etonogestrel implants. Copper-bearing intrauterine devices (Cu-IUDs) and levonorgestrel-releasing intrauterine devices (LNG-IUDs) are also unrestricted, though sexually transmitted infection (STI) risk should be considered before insertion. Additionally, all combined hormonal contraceptives, including combined oral contraceptives (COCs), combined injectable contraceptives (CICs), combined contraceptive patches (P), and combined vaginal rings (CVR), are also categorised as MEC Category 1. The Medical eligibility criteria for contraceptive use (the MEC), fifth edition, offers national policy-makers and family planning programmes a comprehensive set of recommendations on the medical safety of contraceptive methods, allowing for the informed development of national policies, protocols and programmes. In 2017, based on available evidence, the WHO Guideline Development Group (GDG) changed the recommendation for progestogen-only injectables from MEC Category 1 (no restrictions with clarification) to MEC Category 2 (benefits outweigh risks with additional considerations and counseling). However, following the results of a large multinational randomized controlled trial (RCT), WHO convened another guideline development group (GDG) meeting in July 2019, leading to a revision of the MEC guidance. As a result, all hormonal contraceptives and intrauterine devices (IUDs) were reclassified as

MEC Category 1, meaning they can be used without restriction by women at high risk of HIV. Refer table 2 for interpretation and application of the medical eligibility criteria (MEC) categories. [13]

Table 2: Interpretation and Application of the Medical Eligibility Criteria (MEC) Categories

Category	With Good Resources for Clinical Judgment	With Limited Resources for Clinical Judgment
1	Use the method in any circumstances	Yes, use the method
2	Generally use the method	
3	Use of the method not usually recommended unless more appropriate methods are not available or not acceptable	No, do not use the method
4	Method not to be used	

The Food and Drug Administration (FDA) has approved two injectable progestin-only contraceptives, Depo-Provera, an intramuscular injection containing 150 mg/mL of medroxyprogesterone acetate, and Depo-SubQ Provera 104, a subcutaneous formulation that delivers 104 mg/0.65 mL of medroxyprogesterone acetate. The FDA reports that Depo-SubQ Provera 104 and Depo-Provera (medroxyprogesterone acetate) are associated with adverse effects, including bone mineral density loss, thromboembolic events (pulmonary embolism, deep vein thrombosis), anaphylaxis, fluid retention, delayed ovulation, depression, injection site reactions, and bleeding irregularities.

- Depo-SubQ Provera 104: Clinical trials with 2,325 women found the most common side effects (≥5% incidence) were dysfunctional uterine bleeding, headache, weight gain, amenorrhea, and injection site reactions. 9% of participants discontinued treatment, mainly due to bleeding irregularities (3%). Postmarketing data highlight rare but serious risks, including osteoporosis, uterine hyperplasia, and anaphylactic reactions.

- Depo-Provera: A study of 3,900 women over 7 years reported common side effects, including headache (16.5%), abdominal pain (11.2%), nervousness (10.8%), dizziness (5.6%), decreased libido (5.5%), and weight gain (>10 lbs in 37.7% at 24 months). Menstrual irregularities were frequent: bleeding in 57.3% at 12 months (32.1% at 24 months) and amenorrhea in 55% at 12 months (68% at 24 months).

Long-term use of both formulations is linked to bone mineral density loss, requiring close monitoring of at-risk patients. Healthcare professionals should be aware of these risks and report suspected adverse reactions to regulatory authorities. [15,16]

Veisi F et al (2013) conducted a cross-sectional descriptive study in Iran from July 2009 to September 2010 to compare the side effects of two injectable contraceptive methods, Depo-Medroxyprogesterone Acetate (DMPA) and Cyclofem over six months. The study included 250 women (125 per group) aged 18–40 years, with no contraindications, recruited from two healthcare centers. Participants received either monthly Cyclofem or three-monthly DMPA injections, with follow-ups every 30 days. Psychological assessments using the Beck Depression Inventory were conducted at baseline and after six months. Data collection included demographic information and reported side effects such as menstrual irregularities, amenorrhea, weight changes, dyspareunia, vaginal dryness, headaches, and bone pain. Statistical analysis was performed to evaluate differences in adverse effects and overall

acceptability, contributing to comparative safety and tolerability assessments for these contraceptive methods. The mean age was higher in the DMPA group (32.1±5.2) compared to the Cyclofem group (29.9±5.6), and parity was also slightly greater (2.39±1.24 as opposed to 1.5±1). Common side effects in the DMPA group included amenorrhea (74.4%), weight gain (48%), bone pain (24%), and vaginal dryness (10.4%). In contrast, Cyclofem users reported reduced bleeding (37.6%), breast tenderness (20%), and headaches (14.4%). Menstrual changes were the primary reason for discontinuation in both groups (~25%), with additional discontinuation reasons including weight gain (18.6%) and bone pain (23.25%) for DMPA users, and headaches (10.4%) and mood changes (8%) for Cyclofem users. [17]

COST-EFFECTIVENESS

According to the Malaysia Medicines Price Guide (MyPrime), the prices for injectable contraceptive progesterone are listed in the table below:[19]

Table 3: Malaysia Medicines Price Guide (MyPriMe) for Medroxyprogesterone Acetate and Norethisterone Enanthate. [19]

Product registration number	Generic name	Brand name	Packaging description (Per Pack)	Unit (SKU)	Retail price per SKU suggested by product registration holder	Retail price per pack suggested by product registration holder	Price updated year
MAL05061485AZ	Medroxyprogesterone Acetate 150 mg/3ml Injection	Condep injection 50mg/ml (3ml vial)	pack of 1 vial	1	7.30	7.30	2024
MAL19973691AZ	Norethisterone Enanthate 200mg Injection	Depocon injection	pack of 10 ampoule	10	27.34	273.40	2024

Hafiz Harun M et al (2023) conducted a cost-effectiveness evaluation of four widely used reversible contraceptive methods, including the Intrauterine Contraceptive Device (IUCD) Cu-375, etonogestrel implant, depot medroxyprogesterone acetate (DMPA) injectable, and oral contraceptive pills (OCP), in Malaysian government-funded health clinics. Using a Markov model, the study simulated contraceptive use in a cohort of 83,500 women aged 20 to 25 years over five years, analysing costs from the Ministry of Health's perspective. Cost estimation included direct provision costs such as contraceptive supply, healthcare personnel, and medical consultation. Effectiveness was measured in terms of pregnancies averted, considering both "typical use" and "perfect use" failure rates. The incremental cost-effectiveness ratio (ICER) was calculated, with a cost-effectiveness threshold of MYR 50,000 per pregnancy averted. Sensitivity analyses were conducted to assess variations in contraceptive failure rates, costs, and discount rates. Over five years, the provision costs per patient ranged from MYR182.71 to MYR538.92. The IUCD method had the lowest average cost-effectiveness ratio (ACER) at MYR43.77 per pregnancy averted, followed by DMPA injectable at MYR85.19, OCP at MYR100.01, and the implant at MYR127.48. The IUCD was the most cost-saving, with a total cost of MYR15,256,327.52 for 348,579 pregnancies averted, while the implant was the most effective, preventing 352,994 pregnancies at a total

cost of MYR44,999,788.44. The incremental cost-effectiveness ratio (ICER) for the implant was MYR6,736.57 per pregnancy averted compared to IUCD. Sensitivity analyses showed that the total cost of the implant had the greatest impact on ICER, ranging from MYR1,640.59 to MYR11,832.55 per pregnancy averted, followed by IUCD costs (MYR5,008.44 to MYR8,463.83 per pregnancy averted). The effectiveness of IUCD and implant methods also influenced cost-effectiveness, while OCP and DMPA injectable had minimal impact. The author concluded that the subdermal contraceptive implant is the most cost-effective method for reducing unintended pregnancies among Malaysian women of reproductive age. The study found that the implant method costs MYR6,736.57 for each additional pregnancy averted compared to the IUCD method. Among the four methods analyzed, the implant and IUCD were the most cost-effective, while the DMPA injectable and OCP methods were less cost-effective. From the health providers' perspective, assuming a willingness-to-pay (WTP) threshold of MYR50,000, the implant method remains the most cost-effective option. Based on these findings, the implant is strongly recommended to be included in Malaysia's public health clinics alongside the IUCD, DMPA injectable, and OCP. However, the low uptake of the implant method in Malaysia suggests that further research is needed to understand women's preferences and the perceived value of alternative contraceptive options. [20]

Suwantika AA et al (2021) conducted a cost-effectiveness analysis of contraceptive use in Indonesia following the implementation of the national health insurance system from 2014 to 2017. Using a decision tree model, the study compared short-acting reversible contraceptives (SARC), including condoms, pills, and injections, with long-acting reversible contraceptives (LARC), such as implants and intrauterine devices (IUDs), against non-contraceptive use. The analysis was conducted from the payer's perspective, specifically Indonesia's national health insurance system, Badan Penyelenggara Jaminan Sosial (BPJS) Kesehatan. The annual costs per method were estimated at $1.42 for implants, $0.71 for IUDs, $2.89 for pills, $4.25 for injections, and $3.36 for condoms. Effectiveness was measured by pregnancies averted, with contraceptive failure rates ranging from 85.00% for condoms to 99.95% for implants. Between 2014 and 2017, the number of SARC users ranged from 19.18 to 26.87 million, while LARC users fluctuated between 3.34 and 7.92 million, with injections and implants being the most commonly used methods in their respective categories. The total cost of SARC use varied between $75.73 million and $101.92 million annually, representing over 92% of total contraceptive costs, while LARC costs ranged from $3.53 million to $8.49 million. The incremental cost-effectiveness ratio (ICER) per pregnancy averted was lower for LARC ($1.67 for implants and $0.84 for IUDs) compared to SARC ($5.18 for injections, $4.80 for condoms, and $3.76 for pills), demonstrating the superior cost-effectiveness of LARC ($1.25 vs. $4.58). Sensitivity analysis highlighted that contraceptive-costs were the most influential factor affecting ICER outcomes. The study concluded that since the implementation of national health insurance, LARC methods, particularly IUDs, have been more cost-effective than SARC methods. Lower contraceptive costs significantly enhance cost-effectiveness, supporting continued investment in LARC to improve affordability and reduce unintended pregnancies in Indonesia. [21]

CONCLUSION

Based on the above review, only one evidence demonstrated that progestogens particularly medrogestone, injectable medroxyprogesterone acetate, and promegestone found to be associated with increase risk of intracranial meningioma with prolonged use. No other

evidence supporting this risk in different regions was found. According to the NPRA report, no local cases of meningioma have been reported in relation to the use of injectable medroxyprogesterone acetate. Additionally, cost-effectiveness analyses suggest that while DMPA is an affordable contraceptive option, intrauterine devices and implants may provide better long-term value.

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