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Off-label indications of aspirin in gynaecology and obstetrics outpatients at two Chinese tertiary care hospitals: a retrospective cross-sectional study

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ABSTRACT

Objective To investigate the prevalence of off-label aspirin indications and the level of scientific support for off-label indications of aspirin in gynaecology and obstetrics outpatients.

Design A retrospective cross-sectional study.

Setting Two tertiary hospitals (a general hospital and a women and children's specialised hospital) in Xiamen, a city located on the southeastern coast of China.

Participants A total of 4257 prescriptions were included for 2091 female patients aged >18 who visited the gynaecology and obstetrics outpatient clinics and received aspirin treatment.

Outcome measures The primary measure of this study was the proportion of off-label indications and of off-label indications supported by strong scientific evidence. Evidence from clinical guidelines and Micromedex is shown using descriptive statements. On-label indications of drugs in the same class as aspirin were also referred to for off-label aspirin use without strong evidence support.

Results All indications of aspirin on outpatient prescriptions were determined as off-label use in this study. The most frequent off-label indication was recurrent miscarriage (2244 prescriptions, 52.71%). Totally, 30.94% of the prescriptions were supported by strong evidence for indications, including recurrent miscarriage with antiphospholipid syndrome and prophylaxis for pre-eclampsia. No drugs in the same class as aspirin had on-label indications for off-label aspirin use without strong evidence support.

Conclusions This study demonstrated that all indications of aspirin used in gynaecology and obstetrics outpatients at the two tertiary hospitals were off-label and not always supported by strong evidence, implicating that physicians should be cautious when issuing off-label prescriptions. More original clinical research on off-label aspirin use is needed to provide reference for routine clinical practice.

Strengths and limitations of this study

- ► Our study is one of the few research to focus on off-label aspirin indications in gynaecology and obstetrics outpatients.
- ► The off-label indications were determined by whether they were supported by strong scientific evidence from clinical guidelines and Micromedex.
- ► The strong scientific evidence from clinical guidelines and Micromedex could be a reference for physicians to make decisions on off-label aspirin use.
- ► Our study was conducted at two hospitals in Xiamen only and thus failed to include a wider population.
- ► The outcome of off-label aspirin use had not been tracked for a long time in our study due to time constraints.

INTRODUCTION

Off-label prescribing, which is performed beyond the indication, dose, route of administration or targeted patient population listed on the labelling or package insert of a product approved by the Food and Drug Administration (FDA),[1] has been applied by physicians in the USA at a nationwide estimated rate of 21%.[2] Several factors may result in off-label prescribing among physicians. First, on-label indications of drugs fail to treat many diseases. For example, there is no drug with FDA approval for polycystic ovary syndrome and few drugs for treatment of its common symptoms,[3] leading to off-label treatments of patients with such disease. Moreover, when patients suffer from the indicated adverse reactions of a drug, physicians may switch to another treatment involving off-label use. Cost of treatment and medical insurance coverage could also lead to a change in treatment option among patients and physicians. Studies have found that patients with Medicare coverage and payment assistance from a medical charity were less likely to receive off-label prescriptions than patients with private insurance.[4] Besides, regulatory systems such as the agencies in the European Union and the UK prohibited pharmaceutical companies from promoting off-label indications of drugs whose effectiveness and safety had not been confirmed.[5] The gap between delayed

approval and the urgent need for clinical treatment results in off-label prescribing among physicians, who are thus at high legal risk.

It has been found that off-label drug use is associated with adverse drug events (ADEs) in children (a high risk of 7.3% in off-label use vs 1.2% in on-label use)[6] and adults (with adjusted HR of 1.44).[7] However, off-label use supported by strong scientific evidence had a similar risk of ADEs to on-label use,[7] indicating that off-label prescribing may be performed after weighing the benefits versus the risks. The status of evidence supporting off-label use of certain drugs varied among different studies,[8–10] depending on drug category, geographical location of the study and the criteria used to judge scientific evidence. In Quebec, Canada, approximately 16% of off-label use of antidepressants in primary care were supported by strong scientific evidence.[8] For off-label use of anticonvulsant drugs in the Medicaid population in Georgia, USA, 19.09%–57.07% were non-evidence-based.[9] Additionally, our previous study found only 22.75% of off-label use of tamoxifen in a Chinese tertiary care hospital were supported by strong scientific evidence.[10]

Aspirin, initially used as an antipyretic analgesic synthesised in 1897, has been used for over a century for many other indications. It can inhibit the prostaglandin-producing enzyme called cyclo-oxygenase and subsequently reduce inflammation, fever and pain.[11] As a result of reducing platelet aggregation as well, the current on-label use of aspirin focuses on the cardiovascular system to reduce the risk of onset of or death from myocardial infarction and recurrent stroke in high-risk patients.[12] In obstetrics, aspirin is mostly used for prevention of pre-eclampsia and fetal growth restriction. Pre-eclampsia is a hypertensive disorder and is the leading cause of death among Latin American and Caribbean pregnant women.[13] A low dose of aspirin has been proven to protect against vasoconstriction[14] and platelet thromboxane production[15] in pregnancy. A systematic analysis[16] indicated that a low dose of aspirin starting at 16 weeks or earlier could reduce the risk of pre-eclampsia and fetal growth restriction significantly by 53% and 56%, respectively. However, the use of aspirin in women undergoing in vitro fertilisation is a controversial off-label use. The mechanism involved improving uterine and ovarian blood flow[17] and promoting interleukin 3 production,[18] which were believed to increase the success rate of pregnancy. Systematic analyses[19 20] showed similar non-significant outcomes in the rates of live birth and miscarriage when comparing aspirin with no treatment or placebo, but had different conclusions on the rate of clinical pregnancy. Aspirin has also been used off-label in the field of miscarriage[21] and its main cause, that is, antiphospholipid antibody syndrome (APS).[22] Studies[21 23] showed that aspirin did not improve the rate of live births as compared with placebo among women with unexplained recurrent miscarriage or without detectable anticardiolipin antibodies. In contrast, when used in miscarriage with APS, aspirin plus heparin decreased the risk of miscarriage in APS,[24] suggesting that only in certain conditions can aspirin play an important role in the treatment of miscarriage.

Although many studies had been conducted on specific disorders in obstetrics and gynaecology, few data have been reported on the overall off-label use of aspirin in the obstetrics and gynaecology outpatient setting. In addition, in spite of a large number of original clinical research on off-label use, no study has assessed whether it was supported by clinical decision systems or practice guidelines, which were more easily available and understandable for physicians in routine medical practice. Therefore, the aim of this study was to investigate the prevalence of off-label aspirin indications and provide a review on scientific evidence supporting these off-label indications at two hospitals.

METHODS

Study population and setting

This study was conducted at two hospitals, namely the First Affiliated Hospital of Xiamen University (hospital A) and the Women and Children's Hospital, School of Medicine, Xiamen University (hospital B). The First Affiliated Hospital of Xiamen University is a tertiary general hospital with 2500 beds, 4437 staff members and 4.1 million annual outpatient visits. It consists of 59 departments and treats patients of all age groups in the southeastern region of Fujian Province. The Women and Children's Hospital, School of Medicine, Xiamen University is a tertiary specialised hospital in Xiamen with 770 beds, 1100 staff members and 1.5 million annual outpatient visits, covering an area of 63 000 square metres. Its outpatient clinics include obstetrics and gynaecology, reproductive medicine, family planning, general medicine and paediatrics. Visiting patients mostly consist of women and children from the same region as the First Affiliated Hospital of Xiamen University.

Data source

Prescriptions containing aspirin from both hospitals were extracted using the Hospital Information System (HIS) software, which was developed by Zoe. The HIS contains an electronic prescribing subsystem and a drug management subsystem. A prescription must be complete, consisting of information on patient characteristics and pharmacotherapeutic regimens, so that it can be approved by the electronic prescribing subsystem and then accepted by the subsystem at the pharmacies. Patient characteristics refer to name, age, gender and medical record number. Pharmacotherapeutic regimens refer to drug name, strength, dose, route of administration, total amount of drug and price.

Inclusion and exclusion criteria

Prescriptions containing aspirin for treatment of certain conditions from the gynaecology and obstetrics outpatient clinic of both hospitals were included during the

study between 1 January and 31 December 2019. Prescriptions for patients aged less than 18 and with such ambiguous diagnosis as 'routine gynaecological examination' were excluded.

Determination of off-label indications

According to the National Medical Products Administration (NMPA; formerly China Food and Drug Administration), approved indications for aspirin include fever, generalised aches and pains (including headache, arthralgia, migraine, toothache, muscle pain, neuralgia and dysmenorrhoea), unstable angina, rheumatoid arthritis, and prophylaxis for thrombosis after transient ischaemic attack, myocardial infarction, atrial fibrillation, artificial mechanical heart valve replacement surgery or surgery for arteriovenous fistula.

An indication was classified as off-label if it was not among the indications approved by the NMPA as of December 2019. A prescription with multiple indications was classified as off-label use when all indications were outside the scope of the approved indications.

However, there were some conditions where it was hard to identify whether aspirin was used off-label. Therefore, medical records from the two hospitals were screened out where aspirin was only prescribed for some minor symptoms such as headache, toothache or pain in other organs, which physicians might not record in the diagnoses. Previous medical records (if kept completely) were also examined to find out whether patients suffered from cardiovascular diseases which were unrelated to gynaecology and obstetrics during the same period. For example, some women bore children at an old age following the implementation of China's two-child policy, making them vulnerable to cardiovascular diseases. Under this condition, aspirin was used in these patients in an on-label manner. If a patient was diagnosed with unstable angina and pregnancy hypertension, the prescription for this patient would be classified as on-label use rather than off-label, although this seldom happened.

Level of evidence for off-label indications

The term strong evidence was defined as evidence for off-label aspirin use recommended or suggested by published guidelines or documents at Micromedex.

The guidelines chosen for supporting off-label indications were the latest versions (as of March 2020, end of the study period) published by the medical associations in the USA, Britain, European Union or Canada due to their advanced developments in obstetrics and gynaecology. If an indication was recommended or suggested in the chosen guidelines, instead of not mentioned, not recommended, against use, contraindicated or not clear, it was classified as an indication supported by strong evidence. Other evidence was defined as 'weak evidence'.

The recommendations from Micromedex for certain indications were divided into five levels, namely I, IIa, IIb, III and indeterminate, where an off-label use was recommended, recommended in most cases, recommended in some cases, not recommended or without conclusive evidence. In our study, an off-label indication recommended at I–IIa level was defined as supported by strong evidence.

If an off-label indication of aspirin was not supported by strong evidence, our study would determine whether there were other drugs in the same class as aspirin available with an on-label indication for the related off-label use. Drugs with the same former five Anatomical Therapeutic Chemical code letters and numbers as aspirin (ATC code: B01AC06) (eg, platelet aggregation inhibitors, ATC code: B01AC**) were defined as in the same class as aspirin. Off-label use meeting none of these criteria was determined as not supported by strong evidence or on-label indications of drugs in the same class as aspirin.

A total of eight drugs used at the two hospitals were classified as other drugs in the same class as aspirin, including clopidogrel (B01AC02), dipyridamole (B01AC07), carbasalate calcium (B01AC08), indobufen (B01AC10), iloprost (B01AC11), tirofiban (B01AC17), beraprost (B01AC19) and cilostazol (B01AC23). Their on-label use was determined by their drug label.

Evidence was searched using Medical Subject Headings (MeSH) terms combined with synonyms of off-label indications. The search year on PubMed was from 2000 to the end of the study period. The workflow is shown in figure 1.

Statistical analysis

In this study, prescription was adopted as the unit of analysis because one patient might use aspirin for different indications during the study period. The characteristics of the included patients and the prescriptions were presented through descriptive analysis. The proportion of off-label indications was counted as the number of prescriptions with off-label indications divided by the total number of prescriptions containing aspirin. The proportion of off-label indications supported by strong scientific evidence was calculated by the number of off-label prescriptions with strong evidence support divided by the total number of off-label aspirin prescriptions. Subgroup analysis of each off-label indication with strong evidence was performed using X^2 statistics according to different age groups (aged under 35 and older) and study institutions (hospitals A and B) using SPSS (V.25).

Patient and public involvement

This was a retrospective cross-sectional study with prescriptions as the research subject. There was no patient or public involvement in the design, recruitment, reporting or dissemination plans of this research.

RESULTS

Characteristics of included patients and prescriptions at the two hospitals

In total, 2091 patients (1539 at hospital A and 552 at hospital B) receiving 4257 prescriptions with aspirin

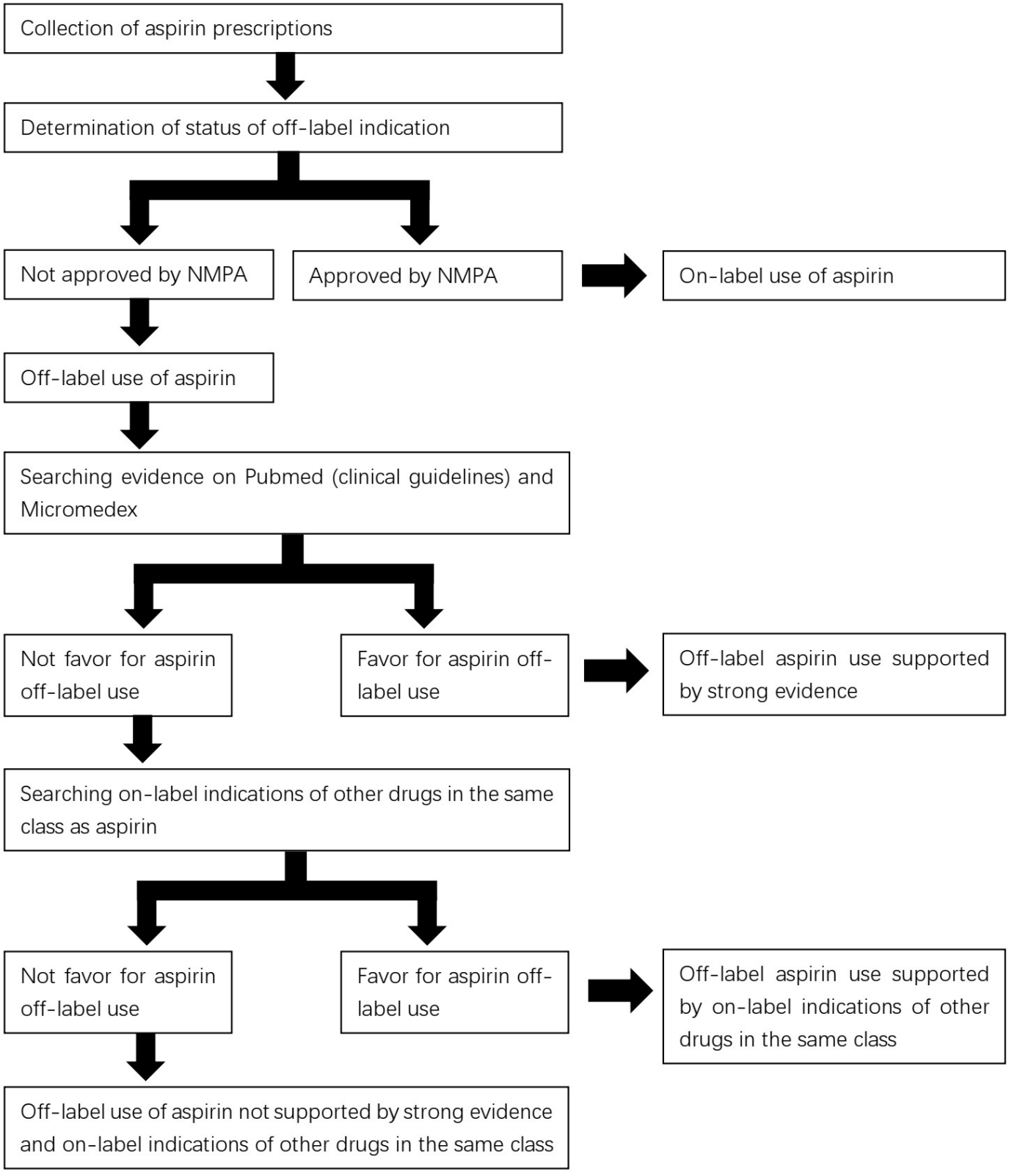

Figure 1 Workflow diagram of our study. NMPA, National Medical Products Administration.

treatment were included in our study during a 1-year period. All included patients were women, with a median age of 31 (IQR 28–35). Patients in the 30–40 years age group (1151 of 2091, 55.05%) accounted for half of the sample.

All aspirin indications at the two hospitals were determined as off-label after the medical records were reviewed. The top three off-label indications were recurrent miscarriage (2244, 52.71%), thrombophilia (346, 8.13%) and antiphospholipid syndrome (321, 7.54%).

The drug orders per prescription ranged from 1 to 8, with an average of 2.25. Prednisone (11.73%) was the most frequently used drug combined with aspirin. The characteristics of the included patients and the prescriptions with off-label aspirin use at the two hospitals are shown in table 1.

Level of scientific evidence for off-label indications

There were nine off-label indications prescribed during the 1-year study, among which seven had been mentioned in the guidelines published on PubMed and three on the documents at Micromedex. In the guidelines, aspirin was recommended for recurrent miscarriage with APS and prevention of pre-eclampsia with risk factors. Only one IIa recommendation at Micromedex was for off-label indication of pregnancy with hypertension, while two IIb recommendations were for female infertility and antiphospholipid syndrome, respectively.

Two off-label indications (tables 2 and 3) were determined to be supported by strong evidence, namely recurrent miscarriage with antiphospholipid syndrome and prophylaxis for pre-eclampsia. A total of 1317 prescriptions contained these off-label indications, accounting for 30.94% of all prescriptions.

On-label indications of other same-class drugs did not cover the off-lable aspirin use that had not been supported by strong evidence.

The subgroup analysis showed that recurrent miscarriage with APS was not associated with age or institutions among all aspirin use in gynaecology and obstetrics ($p>0.05$). However, there could be an association between prophylaxis for pre-eclampsia and these two factors ($p<0.05$) (table 4).

DISCUSSION

Findings of this study

This study demonstrated the prevalence of aspirin use for off-label indications, common off-label use and the level of evidence supporting its use. Recurrent miscarriage was the most common case in off-label use. Nearly one-third of off-label prescriptions were supported by strong evidence. No other drugs in the same class as aspirin were labelled to cover the off-label aspirin use without strong evidence support.

Explanation of the findings

The unexpected result of our study showed that all prescription indications involved off-label use of aspirin. It lies in the fact that aspirin is seldom used for fever or pain relief in China because such alternatives on the market as ibuprofen and acetaminophen can work better. Moreover, most patients at gynaecology and obstetrics clinics are 20–40 years old, who compared with those aged >40 suffer from less cardiovascular diseases which are unrelated to pregnancy. Several other factors could also contribute to the high prevalence of off-label aspirin use in gynaecology and obstetrics. First, there were few other drugs with such on-label indications as miscarriage, antiphospholipid syndrome and prophylaxis for pre-eclampsia in patients with gestational hypertension, for which aspirin was used at a high frequency. Second, aspirin was a cost-effective option as its preventative use in women at high risk of early-onset pre-eclampsia could help save maternal costs of approximately $C14 386 981.80 every year in Canada.[25] Finally, aspirin is an old drug that has been studied in vast numbers of research and has been proven a relatively safe option. Physicians might have little time to track new drugs on the market and be concerned about the lack of safety data on those drugs after a long study period.

As we can see in table 2, three out of five clinical guidelines clearly stated that aspirin is not recommended for treatment of recurrent miscarriage without APS.[26–28] A systematic analysis had found that low molecular weight heparin combining aspirin interventions showed no substantial influence on the rates of miscarriage[29] as well as live birth[30] in patients with unexplained recurrent miscarriage. Antiphospholipid antibodies are associated with high-risk thrombus formation.[31] Aspirin inhibits platelet aggregation and accordingly might reduce the risk of thrombus formation,[32] which may partly explain the benefit of aspirin in the treatment of recurrent miscarriage with APS.

Conditional off-label use of aspirin as prophylaxis for fetal growth restriction exists. Aspirin might reduce the risk of fetal growth restriction in women at high risk of pre-eclampsia[26] or with history of intrauterine growth restriction and pre-eclampsia.[33] Furthermore, the American College of Obstetricians and Gynecologists practice bulletin in 2019 did not even suggest aspirin to be routinely indicated for prevention of fetal growth restriction due to insufficient evidence.[34] In view of the incomplete medical information in the outpatient setting, it was unclear whether patients had a history of fetal growth restriction or that the preventative treatment of fetal growth restriction was based on the risk of pre-eclampsia, so the prescriptions were the same as those for prevention of pre-eclampsia and were therefore not counted in this study.

Our study found no other drugs in the same class as aspirin were labelled to cover the off-label aspirin use without strong evidence support, which might also explain why physicians chose aspirin as a treatment option for no-strong-evidence-support off-label use. Although other drugs in the same class had similar pharmacological effects as aspirin, few studies had been conducted in clinical treatment on them for those indications due to potential differences in clinical risk, such as the harm to fetus. The clinical efficacy of the same-class drugs for those off-label indications was in lack of proof, which went against the assumption that drugs in the same class could be interchangeable.

Although several guidelines support the use of aspirin for prevention of pre-eclampsia and further miscarriage in pregnancy with APS, it had not yet achieved FDA

Table 1 Characteristics of included prescriptions with off-label aspirin use at the two hospitals

	Hospital A			Hospital B			Total		
	Item	n	Proportion (%)	Item	n	Proportion (%)	Item	n	Proportion (%)
Patients		552			1539			2091	
Age group (years)									
18–20		0	0.00		5	0.32		5	0.24
21–30		215	38.95		568	36.91		783	37.45
31–40		285	51.63		866	56.27		1151	55.05
41–50		43	7.79		99	6.43		142	6.79
51–		3	0.54		0	0.00		3	0.14
Prescriptions		1208			3049			4257	
Prescriptions per patient		2.19			1.98			2.04	
Medical orders		2187			7371			9558	
Medical orders per prescription		1.81			2.42			2.25	
Prescriptions with strong evidence*		297	24.59		1020	33.45		1317	30.94
Recurrent miscarriage+APS		31	2.57		63	2.07		94	2.21
Prevention of pre-eclampsia†		295	24.42		1020	33.45		1315	30.89
▶ Any of the high risk factors		110	9.11		546	17.91		656	15.41
▶ Two or more moderate risk factors		199	16.47		510	16.73		709	16.65
Top 5 off-label indications									
	Recurrent miscarriage	561	46.44	Recurrent miscarriage	1683	55.20	Recurrent miscarriage	2244	52.71
	PCOS	114	9.44	Thrombophilia	333	10.92	Thrombophilia	346	8.13
	APS	67	5.55	APS	254	8.33	APS	321	7.54
	IUA	36	2.98	Hypertension	100	3.28	PCOS	177	4.16
	Hypertension	17	1.41	IUA	68	2.23	Hypertension	117	2.75
Common drugs combined									
	Hydroxychloroquine sulfate	290	13.26	Prednisone acetate	1051	14.26	Prednisone acetate	1121	11.73
	Metformin	104	4.76	Vitamin E	954	12.94	Vitamin E	954	9.98
	Prednisone acetate	70	3.20	Folic acid	716	9.71	Folic acid	716	7.49
	Vitamin D	46	2.10	Dydrogesterone	425	5.77	Dydrogesterone	469	4.91
	Dalteparin sodium	46	2.10	Multivitamin	229	3.11	Hydroxychloroquine sulfate	290	3.03
	Dydrogesterone	44	2.01	Low molecular weight heparin	206	2.79	Multivitamins	229	2.40

*The number of prescriptions with strong evidence was calculated when any of the prescriptions for recurrent miscarriage+APS or prevention of pre-eclampsia with risk factors were included.
†The risk factors refer to ACOG guideline: Gestational Hypertension and Pre-Eclampsia.
ACOG, American College of Obstetricians and Gynecologists; APS, antiphospholipid antibody syndrome; IUA, Intrauterine Adhesions; PCOS, polycystic ovary syndrome.

Table 2 Summary of strong evidence for recurrent miscarriage from each guideline

Indication		ACOG[26 40 41]	RCOG[42]	SOCG[27]	ESHRE[28]	ASRM[43]
Miscarriage with APS	Guidelines (year)	▶ Guideline A: Early pregnancy loss (2018). ▶ Guideline B: Antiphospholipid syndrome (2012). ▶ Guideline C: Low-dose aspirin use during pregnancy (2018).	▶ Investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage (2011).	▶ Venous thromboembolism and antithrombotic therapy in pregnancy (2014).	▶ Recurrent pregnancy loss (2017).	▶ Evaluation and treatment of recurrent pregnancy loss: a committee opinion (2012).
	Recommendations	▶ Guideline A: Anticoagulants, aspirin or both for women with antiphospholipid syndrome have been shown to reduce the risk of early miscarriage. ▶ Guideline B: Women with APS and a history of stillbirth or recurrent miscarriage but no history of thrombosis should prophylactically use heparin and low-dose aspirin during pregnancy and 6 weeks post partum. ▶ Guideline C: For women with antiphospholipid syndrome, treatment combining low-dose aspirin and unfractionated heparin or low molecular weight heparin has been shown to reduce the risk of early miscarriage.	▶ Pregnant women with antiphospholipid syndrome should consider low-dose aspirin plus heparin treatment for further miscarriage prevention.	▶ Pregnant women with confirmed antiphospholipid syndrome should use low-dose aspirin or low-dose aspirin plus low molecular weight heparin.	▶ Women who meet the APS laboratory criteria and have a history of three or more miscarriages should receive low-dose aspirin (75–100 mg/day) before conception, and prophylactic dose heparin or low molecular weight heparin from the day the pregnancy test is positive.	▶ Women whose titres of circulating antiphospholipid antibodies were persistent and at medium to high level should receive prophylactic dose of unfractionated heparin plus low-dose aspirin.
Miscarriage without APS	Guidelines (year)	▶ Low-dose aspirin use during pregnancy (2018).	NA.	▶ Venous thromboembolism and antithrombotic therapy in pregnancy (2014).	▶ Recurrent pregnancy loss (2017).	NA.
	Recommendations	▶ For women without antiphospholipid syndrome, low-dose aspirin has not been proven for prevention of unexplained early pregnancy loss.	NA.	▶ Women with a history of recurrent miscarriage but no confirmed antiphospholipid syndrome are not recommended to receive low-dose aspirin plus low molecular weight heparin.	▶ Women with unexplained RPL are not recommended to use heparin or low-dose aspirin due to the evidence that they do not improve rate of live births.	NA.

ACOG, American College of Obstetricians and Gynecologists; APS, antiphospholipid antibody syndrome; ASRM, American Society for Reproductive Medicine; ESHRE, European Society of Human Reproduction and Embryology; NA, not available; RCOG, Royal College of Obstetricians and Gynaecologists; RPL, Recurrent Pregnancy Loss; SOGC, Society of Obstetricians and Gynaecologists of Canada.

Table 3 Summary of strong evidence for prevention of pre-eclampsia from each guideline

	ACOG[44 45]	USPSTF[46]	SOCG[47]	ISSHP[48]
Guidelines (year)	▶ Guideline A: Chronic hypertension in pregnancy (2019). ▶ Guideline B: Gestational hypertension and pre-eclampsia (2019).	▶ Low-dose aspirin use for the prevention of morbidity and mortality from pre-eclampsia: US Preventive Services Task Force recommendation statement (2014).	▶ Diagnosis, evaluation and management of the hypertensive disorders of pregnancy: executive summary (2014).	▶ Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice (2018).
Clinical risk assessment for pre-eclampsia	*High risk factors:* ▶ Previous pregnancy with pre-eclampsia. ▶ Multifetal gestation. ▶ Renal disease. ▶ Autoimmune disease. ▶ Type 1 or type 2 diabetes mellitus. ▶ Chronic hypertension. *Moderate risk factors:* ▶ First pregnancy. ▶ Maternal age ≥35 years. ▶ BMI >30. ▶ Family history of pre-eclampsia. ▶ Sociodemographic characteristics. ▶ Personal history factors.	▶ Same as ACOG.	*Risk factors in the following parts:* ▶ Demographics and family history. ▶ Medical or obstetric history. ▶ Current pregnancy.	▶ Prior pre-eclampsia. ▶ Chronic hypertension. ▶ Multiple gestation. ▶ Pregestational diabetes. ▶ Maternal BMI >30. ▶ Antiphospholipid syndrome/ SLE. ▶ Assisted reproduction therapies.
Recommendations	▶ Guideline A: Women with chronic hypertension should start low-dose aspirin (81 mg) daily between 12 and 28 weeks of gestation (preferably before 16 weeks) until delivery. ▶ Guideline B: Women with any high risk factors or with more than one intermediate risk factor should receive low-dose (81 mg/day) aspirin, initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) until delivery for pre-eclampsia prophylaxis.	▶ Women at high risk should use low-dose aspirin (81 mg/day) for pre-eclampsia prophylaxis after 12 weeks of gestation.	▶ Women at high risk should take aspirin at a low dose (75–162 mg/day) at bedtime for prevention of pre-eclampsia after the diagnosis of pregnancy but before 16 weeks of gestation until delivery.	▶ Women with established strong clinical risk factors should be treated by low-dose aspirin (75–162 mg/day) before 16 weeks but definitely before 20 weeks.

ACOG, American College of Obstetricians and Gynecologists; BMI, Body Mass Index; ISSHP, International Society for the Study of Hypertension in Pregnancy; SLE, Systemic Lupus Erythematosus; SOCG, Society of Obstetricians and Gynaecologists of Canada; USPSTF, US Preventive Services Task Force.

approval. No consensus had been reached on the safety of aspirin. The FDA was warning to avoid the use of NSAIDs in pregnancy at 20 weeks or later because of the risk of kidney problems. leading to low levels of amniotic fluid surrounding unborn babies. However, this warning does not apply to low-dose aspirin in certain conditions.[35] Besides, pharmaceutical companies were reluctant to continue investing heavily in related clinical trials because aspirin had gained huge profits in the prevention and treatment of cardiovascular diseases. They had no legal obligation to resubmit a new indication for approval[36] and were unwilling, to some extent, to do so since aspirin had come off-patent. The slow progress approval process of FDA for a new indication after long-term clinical trials would result in off-label use as welll. These factors hindered getting FDA approval for indications supported by clinical guidelines.

Table 4 Subgroup analysis of indications with strong evidence

	Recurrent miscarriage with APS				Prophylaxis for pre-eclampsia			
	Cases	Not cases	Proportion (%)	P value	Cases	Not cases	Proportion (%)	P value
Age groups (years)								
18–35	66	3090	2.09	0.38	471	2685	14.92	<0.05
Above 35	28	1073	2.54		844	257	76.66	
Institutions								
Hospital A	31	1177	2.57	0.32	295	913	24.42	<0.05
Hospital B	63	2986	2.07		1020	2029	33.45	

APS, antiphospholipid antibody syndrome.

Comparison with similar studies

To our knowledge, there were few published studies investigating off-label uses of aspirin, except two in Chinese journals. Sun[37] found that the most frequent use of aspirin at an obstetrics and gynaecology hospital was for female infertility. However, the highest frequency of off-label aspirin use was in recurrent miscarriage in a study by He *et al*[38] at a general hospital setting. Such a result reflected a setting difference between general hospitals and specialised ones in the use of aspirin for its off-label indications. Additionally, these two studies did not present the prevalence of evidence support them, which could not provide the degree of reliability of off-label use.

Strengths and limitations

Our study was among the few to investigate the prevalence of off-label aspirin use. The references for determining the status of evidence support were chosen from the decision support system of Micromedex and from public guidelines, which were evidence-based and were more easily available and practical for making decisions than primary research studies in terms of saving time to analyse and understand. It is expected that this approach could be applied to review off-label use of other drugs.

Several limitations were noteworthy. First, the data in our study were collected from only two institutions, failing to cover a wider population from other regions. Moreover, it could not be identified whether off-label prescribing was based on the awareness of the effectiveness and safety profile of off-label indications, or on such conditions as encountering adverse reactions from other drugs with on-label indications. In addition, there was lack of follow-up of the clinical outcomes of off-label use in patients due to the nature of a cross-sectional study, where measurements of members of the sample were obtained at a single point in time.[39] Therefore, it is association not causation that could be inferred from the conclusions of such a cross-sectional study. As we have found, the prevalence of off-label use with strong evidence support (prophylaxis for pre-eclampsia) may be associated with age and institutions. Besides, due to time constraints, rather than off-label dose, frequency or duration, our study only investigated whether the off-label indications were supported by strong evidence.

CONCLUSIONS

Our study investigated the common off-label indications of aspirin used at a specialised hospital and a general hospital and found them not always supported by strong evidence. Nearly two-thirds of treatments lacked strong evidence supporting off-label aspirin use, exposing physicians to medical risks. Besides, no alternative drugs in the same class as aspirin were labelled for off-label aspirin use which had not been supported by strong evidence. It would be meaningful to summarise the evidence on off-label use of aspirin and integrate them into the prescribing system, with a view to provide physicians access to evidence before making clinical decisions. Further studies should be carried out to evaluate the benefit, risk and cost of off-label aspirin use for reference.

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