Sildenafil in Pregnancy: A Systematic Review of Maternal Tolerance and Obstetric and Perinatal Outcomes

Liam Dunn^a Ristan Greer^a Vicki Flenady^a Sailesh Kumar^{a–c}

^aMater Research Institute, University of Queensland, ^bMater Mothers' Hospital, and ^cSchool of Medicine, University of Queensland, Brisbane, QLD, Australia

Keywords

Sildenafil citrate · Placental insufficiency · Fetal hypoxia · Fetal therapies · Pregnancy

Abstract

Introduction: This systematic review evaluates maternal tolerance and obstetric and perinatal outcomes following sildenafil citrate (SC) use in human pregnancy. **Data Sources:** Scopus, PubMed, Cochrane Library, Web of Science, Embase, and Google Scholar were searched. Relevant full-text studies including case series and reports in English were included. Publications were excluded if the pregnancy was terminated or if SC was used only at conception. **Results:** Sixteen studies were included ($n = 165$). Indications for use and outcomes were variably reported. Maternal outcomes reported were headache (45.8%, 49/107), visual disturbances (17.3%, 14/81), dyspepsia/epigastric pain (15.8%, 15/95), and hypotension (0%, 0/39). There were more caesarean (83.3%, 55/66) than vaginal deliveries (16.7%, 11/66) and postpartum haemorrhage occurred in 3.9% (3/76) of women exposed to SC. Neonatal outcomes including nursery admission (67.3%, 35/52), Apgar scores <7 at 5 min (7.1%, 4/56), and cord arterial pH <7.1 (0%, 0/17) were reported. Stillbirths (4.3%, 3/69) and neonatal deaths (3.9%,

5/129) were comparable to SC-naïve groups. There were no congenital malformations (0%, 0/35). **Conclusions:** Despite limited data, overall there does not appear to be any severe adverse maternal side effects nor any increase in the rate of stillbirths, neonatal deaths, or congenital anomalies attributed to SC.

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Background

Sildenafil citrate (SC) is a phosphodiesterase-5 (PDE-5) inhibitor. It acts by preventing the degradation of the second messenger cyclic guanosine 3',5'-monophosphate by the enzyme PDE-5. This results in increased nitric oxide production and consequent vascular smooth muscle relaxation and an increase in vasodilation [1]. Due to its preferential vasodilatory effects on pelvic vasculature, SC is now a well-established treatment for erectile dysfunction in males [2] and this remains its most common indication for use. It has also been trialled in children [3–5] and pregnant women [6–8] with pulmonary hypertension (PH).

The vasodilatory effects of SC also manifest on uterine and myometrial vessels [9–11], which results in increased

uterine flow [12, 13] and endometrial thickening [11, 14] putatively promoting an increase in fetal weight [15]. Its use in human pregnancy has largely been restricted to a few specific maternal indications, including severe PH [16–22] or preeclampsia (PET) [23, 24], and as an adjunct to presumed inadequate uteroplacental perfusion [13, 25] and severe early-onset fetal growth restriction (FGR) [12, 26–29]. This in turn has led to a current ongoing multi-centre randomised controlled trial (RCT) of SC for the treatment of severe FGR [30].

To date, the use of SC in human pregnancy has been confined to relatively small RCTs and case series and reports.

Objective

There is increasing interest in, and use of, SC as a therapeutic option for PH, PET, and FGR. The purpose of this systematic review was to collate the current evidence in relation to maternal tolerance and side effects, and obstetric and perinatal outcomes following the use of SC in human pregnancy.

Data Sources

An online database search for all relevant publications from the past 30 years was undertaken by the authors and institutional research librarian in July 2016. Databases included Scopus, PubMed, Cochrane Library, Web of Science, Embase, and Google Scholar. Keywords and MeSH terms used included: “sildenafil citrate”, “Viagra®”, “phosphodiesterase-5 inhibitor”, “pregnancy”, “labor”, “preeclampsia”, “hypertension”, “fetal growth restriction”, “pulmonary hypertension”, “mode of delivery”, “hypotension”, “haemorrhage”, “visual disturbances”, “fetus”, “newborn”, “neonate”, “Apgar”, “perinatal death”. All publications reporting the use of SC in human pregnancy with full text or abstract written in English and available electronically were collated for review.

The population of interest was pregnant women who were exposed to SC compared to no SC or placebo. All titles and abstracts were independently reviewed by authors L.D. and S.K. to exclude duplicated and ineligible manuscripts. Systematic and expert reviews, abstracts, book chapters, opinion pieces, and guidelines were excluded. Publications were also excluded if the reported pregnancy was terminated or if SC was only used during peri-conception and not during pregnancy. A manual

Fig. 1. Selection of studies. TOP, termination of pregnancy; RCTs, randomized controlled trials.

search of the reference lists of primary articles was carried out to identify relevant articles not captured in the initial electronic searches. Where possible, authors were contacted for clarification of reported data.

Relevant standards of reporting for each publication type [31–33] were referenced as was the Preferred Reporting for Systematic Reviews and Meta-Analyses statement [34]. Case series [35] and case reports [31] were critically evaluated and included if the outcomes of interest were detailed and provided relevant information on the topic. This was a pragmatic decision given the rarity of SC use in pregnancy.

Results

The flow of identification of relevant studies is shown in Figure 1. Seven hundred and forty-nine publications were initially retrieved using the abovementioned methodology. After all abstracts were screened, 20 full-text articles were reviewed. Three of these publications were excluded because full-text versions were not accessible in English [36–38] and one case report was excluded because it involved a therapeutic second-trimester termination of pregnancy [39].

The final number of publications included for analysis in this systematic review was 16, comprising 165 preg-

Table 1. Summary of included studies

First author, year [Ref.]	Publication	Country	Indication	Cohort size	Maternal age, years	SC regimen	SC duration, days	GA at SC start, weeks
Trapani, 2016 [24]	RCT	Brazil	PET	50	25.3±5.4	50 mg PO 8-hourly	14.4 ^b	29.1±2.1
Trapani, 2016 [29]	RCT	Brazil	FGR	12	23.6±6.2	50 mg PO ^a	NR	28.5±2.1
Dastjerdi, 2012 [12]	RCT	Iran	FGR	14	25.6±1.5	50 mg PO once	1	35±2
Samangaya, 2009 [23]	RCT	UK	PET	17	28 (24–34)	20–80 mg PO 8-hourly	4 [1–15]	31.4 (26.6–32.5)
El-Far, 2014 [25]	Non-RCT	Egypt	URSM	40	*	25 mg PV 6–8-hourly	13 or 24	<13
von Dadelszen, 2011 [26]	Case controlled	Canada	FGR	10	34 (25–40)	25 mg PO 8-hourly	31.5 (9.5–81)	22.4
Subbaiah, 2013 [16]	Cohort	India	PH	4	NR	20 mg PO 8-hourly	NR	NR
Duarte, 2013 [17]	Case series	USA	PH	4	23.5 [19–34]	20–50 mg PO	66.5 [49–196]	25.5 [6–29]
Kiely, 2010 [18]	Case series	UK	PH	3	23 [21–38]	25 mg PO 8-hourly	7 [7–238]	31 [0–33]
Goland, 2010 [19]	Case series	USA	PH	2	21; 30	25–50 mg PO 8-hourly	7; 31	36; 32
El-Far, 2009 [13]	Case series	Egypt	URSM	4	27 [22–30]	25 mg PV 6-hourly	23 [20–24]	9 [6–11]
Panda, 2014 [27]	Case report	India	FGR	1	32	50 mg PO 8–12-hourly	21	26.6
Lin, 2012 [28]	Case report	Taiwan	FGR	1	30	25 mg PO 8-hourly	48	26
Ng, 2012 [20]	Case report	Singapore	PH	1	30	25 mg PO 8-hourly	1	35
Molelekwa, 2005 [21]	Case report	Ireland	PH	1	23	NR	14	28
Lacassie, 2004 [22]	Case report	Chile	PH	1	22	50–150 mg PO daily	98	0 ^c

Data are mean ± standard deviation, median (interquartile range), or median [range]. * Maternal age (median [range]) reported for each SC cohort: 27 years [19–35] and 26.5 years [20–33]. ^a Frequency not reported. ^b Average duration of SC dosing. ^c SC 50 mg PO daily from conception until 9 weeks and then recommenced at 31 weeks until delivery at 36 weeks. RCT, randomised controlled trial; Non-RCT, non-randomised controlled trial; SC, sildenafil citrate; PET, preeclampsia; FGR, fetal growth restriction; URSM, unexplained recurrent spontaneous miscarriage; PH, pulmonary hypertension; NR, not reported; PO, per oral; PV, per vaginal; GA, gestational age.

nancies in total. These included 4 RCTs, 1 non-RCT, 1 case-controlled, 1 cohort, 4 case series, and 5 case reports (Table 1). Data on the number of participants exposed to SC, gestational age at exposure to SC, indication for and duration of SC use, as well as dosage and route of administration were collected (Table 1). Outcomes examined included maternal (hypotension, visual disturbances, headache, dyspepsia/epigastric pain) (Table 2), obstetric (mode of delivery, postpartum haemorrhage), and perinatal (gestational age at delivery, birthweight, Apgar score, acidosis at birth [cord artery pH <7.1], nursery admission, congenital anomalies, stillbirth, and neonatal death) (Table 3). Not all outcomes relevant to this review were reported by each publication.

Hypotension

Nine studies [13, 17, 19, 20, 22–24, 26, 29] (79 pregnancies) reported information on maternal blood pressure. Three RCTs [23, 24, 29] reported significant reductions in maternal blood pressure amongst women with PET. Only one [23] of these RCTs in addition to other studies [13, 17, 19, 20, 22, 26], however, reported sufficient data to estimate the overall rate of hypotension (0%, 0/39).

Visual Disturbance

Of the 4 studies [13, 23, 24, 26] (81 pregnancies) that reported on visual disturbances, 2 RCTs [23, 24] detailed 14 women (17.3%, 14/81) who were affected by visual disturbances. However, in both of these RCTs, visual disturbances occurred at similar rates to those in the placebo groups and no participant withdrew because of visual disturbances [23, 24].

Headache

The overall rate of headache was 45.8% (49/107) as documented in 6 studies [12, 13, 23, 24, 26, 29]. This appeared to be the more commonly reported maternal symptom. In 4 RCTs [12, 23, 24, 29], rates of headache were comparable between the SC and the control groups.

Dyspepsia and Epigastric Pain

In 5 studies [12, 13, 23, 24, 26], the overall rate of dyspepsia and epigastric pain was 15.8% (15/95). Three RCTs [12, 23, 24] did not report any difference in rates of dyspepsia or epigastric pain between SC and control groups.

Other Maternal Symptoms

Information about other maternal symptoms in 147 pregnancies was obtainable from 7 studies [12, 13, 23–26,

Table 2. Maternal tolerance outcomes following sildenafil citrate use in pregnancy

First author, year [Ref.]	Indication	Hypotension	Visual disturbances	Headache	Dyspepsia/epigastric pain
Overall rate (%)	–	0/39 (0)	14/81 (17.3)	49/107 (45.8)	15/95 (15.8)
Trapani, 2016 [24]	PET	NR	10/50	32/50	10/50
Trapani, 2016 [29]	FGR	NR	NR	2/12	NR
Dastjerdi, 2012 [12]	FGR	NR	NR	1/14	0/14
Samangaya, 2009 [23]	PET	0/17	4/17	14/17	5/17
El-Far, 2014 [25]	URSM	*	*	*	*
von Dadelszen, 2011 [26]	FGR	0/10 ^a	0/10 ^a	0/10 ^a	0/10 ^a
Subbaiah, 2013 [16]	PH	NR	NR	NR	NR
Duarte, 2013 [17]	PH	0/4	NR	NR	NR
Kiely, 2010 [18]	PH	NR	NR	NR	NR
Goland, 2010 [19]	PH	0/2 ^b	NR	NR	NR
El-Far, 2009 [13]	URSM	0/4 ^c	0/4 ^c	0/4 ^c	0/4 ^c
Panda, 2014 [27]	FGR	NR	NR	NR	NR
Lin, 2012 [28]	FGR	NR	NR	NR	NR
Ng, 2012 [20]	PH	0/1	NR	NR	NR
Molelekwa, 2005 [21]	PH	NR	NR	NR	NR
Lacassie, 2004 [22]	PH	0/1	NR	NR	NR

PET, preeclampsia; FGR, fetal growth restriction; URSM, unexplained recurrent spontaneous miscarriage; PH, pulmonary hypertension; NR, not reported. * “Commonly recorded adverse effects” reported in 27/40 (67.5%) but no “serious adverse effects”. ^a No “adverse maternal side effects”. ^b “Uneventful” delivery and “stable” postpartum. ^c “No complications or side effects” from antenatal SC.

Table 3. Obstetric and perinatal outcomes following sildenafil citrate use in pregnancy

First author, year [Ref.]	Indication	Caesarean section	Vaginal delivery	Postpartum haemorrhage	Apgar <7 at 5 min	Cord arterial pH <7.1	Nursery admission	Con-genital anomaly	Stillbirth	Neonatal death
Overall rate (%)	–	55/66 (83.3)	11/66 (16.7)	3/76 (3.9)	4/56 (7.1)	0/17 (0)	35/52 (67.3)	0/35 (0)	3/69 (4.3)	5/129 (3.9)
Trapani, 2016 [24]	PET	42/50	8/50	1/50	4/50	NR	33/50	^d	NR	2/50
Trapani, 2016 [29]	FGR	NR	NR	NR	NR	NR	NR	^d	NR	0/12
Dastjerdi, 2012 [12]	FGR	NR	NR	NR	NR	NR	NR	^d	NR	NR
Samangaya, 2009 [23]	PET	NR	NR	1/17	NR	0/17	NR	NR	0/17	1/17
El-Far, 2014 [25]	URSM	NR	NR	NR	NR	NR	NR	0/24	0/24	0/24
von Dadelszen, 2011 [26]	FGR	NR	NR	NR	NR	NR	NR	^b	3/10	2/10
Subbaiah, 2013 [16]	PH	1/2	1/2	0/4	NR	NR	NR	0/4	0/4	0/4
Duarte, 2013 [17]	PH	4/4	0/4	NR	NR	NR	NR	NR	0/4	0/4
Kiely, 2010 [18]	PH	2/3	1/3	NR	0/2	NR	NR	0/3	0/3	0/3
Goland, 2010 [19]	PH	2/2	0/2	0/2 ^a	0/1	NR	NR	0/1	0/2	0/2
El-Far, 2009 [13]	URSM	NR	NR	NR	NR	NR	NR	NR	NR	NR
Panda, 2014 [27]	FGR	1/1	0/1	NR	NR	NR	1/1	0/1	0/1	0/1
Lin, 2012 [28]	FGR	1/1	0/1	NR	0/1	NR	NR	NR	0/1	0/1
Ng, 2012 [20]	PH	0/1	1/1	0/1	0/1 ^c	NR	NR	0/1	0/1	NR
Molelekwa, 2005 [21]	PH	1/1	0/1	1/1	NR	NR	1/1	0/1	0/1	0/1
Lacassie, 2004 [22]	PH	1/1	0/1	0/1 ^b	0/1	NR	NR	NR	0/1	NR

PET, preeclampsia; FGR, fetal growth restriction; URSM, unexplained recurrent spontaneous miscarriage; PH, pulmonary hypertension; NR, not reported. ^a “Uneventful” delivery and “stable” postpartum. ^b “Uneventful” delivery. ^c “Baby was healthy with an Apgar score of 9” (time not specified). ^d Exclusion criteria in these studies.

29] with reassuring outcomes. Vomiting, dizziness, diarrhoea, neurological symptoms, facial flushing, and arthralgia and myalgia were reported by the 4 RCTs [12, 23, 24, 29] with similar rates in both the SC and control groups. Additional information on maternal tolerance to SC was reported in 3 other studies [13, 25, 26]. The specific nature of the side effects and their rates of occurrence in these studies, however, were not consistently reported, though none were described as severe [13, 25, 26].

Mode of Delivery

Ten studies [16–22, 24, 27, 28] reported the modes of delivery for 66 pregnancies. The overall rates for caesarean (CS) and vaginal births (including instrumental births) were 83.3% (55/66) and 16.7% (11/66), respectively. Indication for delivery was not consistently reported across all studies, however; 16.4% (9/55) of CS were performed for severe PH [16–19], 3.6% (2/55) were performed for FGR [27, 28], and 3.6% (2/55) were performed for overlapping serious maternal and fetal indications [21, 22].

Postpartum Haemorrhage

The overall postpartum haemorrhage rate, reported in 7 studies [16, 19–24], was 3.9% (3/76). In 2 of the larger RCTs [23, 24], postpartum haemorrhage rates were similar in both the SC and the control groups.

Gestational Age at Delivery and Birthweight

The gestational age at birth following antenatal SC exposure varied from 27 weeks [26] to 37 weeks [19], as reported for 76 babies in 11 studies [16–22, 24, 26–28]. Birthweights for 77 babies were reported across 9 publications [16, 18, 19, 21–24, 27, 28]. The minimum and maximum reported birthweights were 553 g [23] and 2,480 g [23], respectively. However, there was incomplete data regarding the range of birthweights and corresponding gestational age at birth for the other studies.

Apgar <7 at 5 min

Six publications [18–20, 22, 24, 28] reported Apgar scores of 56 babies. Of these, there were 4 cases of Apgar scores <7 at 5 min (7.1%, 4/56) that were all reported in 1 RCT [24]. The same RCT also reported a lower rate of Apgar scores <7 at 5 min in the SC group compared to the placebo group (8%, 4/50 vs. 12%, 6/50) [24].

Cord Arterial pH <7.1

Only one study reported cord arterial pH in babies born to mothers who had received SC antenatally [23]. None of the 17 babies in the SC cohort had cord arterial pH <7.1.

Furthermore, there were no clinically important differences in the median cord arterial pH of the SC (7.25, range: 7.17–7.31) and the placebo (7.29, range: 7.26–7.3) groups [23].

Admission to Neonatal Intensive Care Unit

Thirty-five babies (67.3%, 35/52) were admitted to the neonatal intensive care unit, reported in 1 RCT [24] and in 2 case reports [21, 27]. Although not powered to detect differences in neonatal outcomes, Trapani et al. [24] observed a lower incidence of neonatal intensive care unit admissions amongst babies born in the SC cohort compared to placebo (66%, 33/50 vs. 74%, 37/50). The indications for admission were not specified, though overall rates of other important neonatal outcomes (infection, intraventricular haemorrhage, and respiratory distress) were reported in the study with no significant differences between the SC and placebo groups [24].

Congenital Anomalies

Seven publications [16, 18–21, 25, 27] that included 35 babies reported no congenital anomalies. Three RCTs [12, 24, 29] excluded pregnancies with known fetal anomalies and, along with another RCT [23], did not report on presence or absence of fetal or congenital anomalies at birth. Consequently, these studies did not contribute to the overall rate of congenital anomalies.

Stillbirth and Neonatal Death

Fourteen studies [16–29] reported stillbirth and neonatal deaths. Overall rates of stillbirth and neonatal death were 4.3% (3/69) and 3.9% (5/129), respectively. Whilst the specific causes for perinatal mortality were not consistently reported, rates were comparable between SC and control groups. It is likely that the rates were confounded by the effects of extreme prematurity as well as the severity of FGR and maternal PET.

Discussion

This systematic review summarises the available literature reporting clinically relevant outcomes following SC use in pregnancy. The outcomes reported in this systematic review are constrained by the paucity of studies and the limited information provided in many of these reports. Nevertheless, it appears that at the very least, maternal tolerance and perinatal outcomes following SC use in pregnancy are comparable with controls.

The available evidence so far suggests that SC is safe in pregnancy and this underpins its potential as a therapy

for selected maternal and fetal disorders. More than 130 *in vivo* animal and *ex vivo* toxicology, pharmacology, and toxicokinetic studies have demonstrated a good safety profile for SC with no increase in teratogenic sequelae [40]. Consistent with this, no congenital anomalies were reported in our systematic review.

In terms of maternal side effects and tolerance in human pregnancy, less data is available. Information about these outcomes has largely been drawn from studies involving SC for erectile dysfunction and PH. A review of 63 double-blind RCTs reported the safety of SC in males with erectile dysfunction for key outcomes like cardiovascular risks, visual disturbances, and tolerability with reassuring results [41]. Other studies involving males with erectile dysfunction suggest the most common side effects are those related to the pharmacology of PDE-5 inhibition and include headache, facial flushing, nasal congestion, and dyspepsia [42–45].

Maternal side effects from SC presented in our review are comparable to previously published data from non-pregnant populations [25, 26, 46]. Overall, side effects to SC in pregnancy appear mild. There was only one case in our review where a participant required an SC dose down-titration due to dyspepsia [23] and another case where the participant withdrew due to severe headache and facial flushing [24]; both of these, however, occurred in the context of PET. Such side effects also appear to be reported at similar rates in pregnant women not exposed to SC [12, 23, 24, 29] making conclusions regarding a causal effect difficult.

The obstetric and perinatal outcomes observed in this review could likely be explained by the severe maternal and fetal conditions. Amongst the studies included in this review, the indications for SC varied, as did the route, dosage, and frequency of SC administration. Overall, 165 participants received SC for PH, PET, FGR, and fertility. It is likely that the maternal and uteroplacental circulatory changes in these pregnancies could vary substantially due to different underlying pathophysiological processes. The observed stillbirth and neonatal deaths occurred at similar rates in both the SC and control groups. These were largely attributed to the severe maternal and fetal conditions which in some cases necessitated extreme premature delivery. Because of these factors, mode of delivery was often by planned CS, making firm conclusions regarding the effect of SC on the mode of delivery problematic. Nevertheless, the limited available data suggests that vaginal birth is not contraindicated when on SC therapy. Furthermore, the overall postpartum haemorrhage rate observed in this review was comparable to that

amongst both control cohorts and the broader population [47].

The limitations of this systematic review relate mainly to the novelty of SC use in pregnancy. Although the publications included in this review reported clinically relevant outcomes, all were of small numbers and inadequately powered for rare adverse events and this remains a source of bias. Publications included in this review were limited mostly to case reports, case series, and small cohort studies, with just 3 relatively small RCTs, amongst which there was little longer-term data reported for neurodevelopmental outcomes. The included publications also did not uniformly report on all of the outcomes and this therefore limited the number of cases available for pooling of data. In some studies, outcomes were not reported for the entire cohort and consequently some studies lacked consistent, uniform reporting standards [31–35].

SC is amongst a number of novel therapies whose effects on improving placental function are currently being investigated. Samangaya et al. [23] were the first to document the pharmacokinetics of SC in human pregnancy in their double-blind RCT. They demonstrated that SC was metabolised more rapidly in pregnancy to its less efficacious form, desmethyl-sildenafil [23]. Some authors [10, 23] suggest that the altered plasma volume and pH in pregnancy necessitates higher doses of SC to reach a therapeutic plasma concentration. In line with this, a subsequent double-blind RCT by Trapani et al. [24] utilised a higher SC dose regimen of 50 mg 8-hourly amongst participants with PET. When compared to placebo, they demonstrated a benefit of pregnancy prolongation as well as no worsening of maternal side effects [24]. The STRIDER study is a double-blind RCT investigating the effect SC has on improving fetal growth in pregnancies complicated by early-onset severe growth restriction [30]. Another double-blind RCT currently underway is investigating if SC administered intrapartum can reduce the risk of emergency CS for fetal compromise amongst term, appropriately grown babies [48]. Both of these studies also use an SC regimen of 50 mg orally 8-hourly. Further information regarding the safety profile of SC in pregnancy may be likely once these studies are published.

This review provides current information on clinically relevant outcomes following SC use during pregnancy. Overall, there does not appear to be severe adverse maternal side effects reported nor any increase in the rate of stillbirths, neonatal deaths, or congenital anomalies attributed to SC. Given the limited available information, consideration should be given to a registry-based approach for documenting outcomes of pregnancies on SC.

Acknowledgment

This work was funded by the Mater Foundation.

Disclosure Statement

The authors report no conflicts of interest.

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