SILDENAFIL USE DURING PREGNANCY FOR SEVERE INTRAUTERINE GROWTH RESTRICTION: A CASE SERIES AND REVIEW OF LITERATURE

Léveillée D, Pharm. D candidate, Pharmacy Department and Pharmacy Practice Research Unit, CHU Sainte-Justine, Montreal, Quebec, Canada, **Iglesias** MH, M.D., F.R.C.S.C, Department of Obstetrics and Gynaecology, CHU Sainte Justine, Montréal, Quebec, Canada
Brochet, MS, B.Pharm., M.Sc., Pharmacy Department, CHU Sainte Justine, Montréal, Quebec, Canada, **Ferreira** E, B.Pharm., M.Sc., Pharm.D., F.C.S.H.P., Faculty of pharmacy, University of Montreal, Pharmacy Department, CHU Sainte Justine, Montréal, Quebec, Canada

Background

- **Severe intrauterine growth restriction (IUGR)**
  - Second trimester onset
  - Estimated fetal weight <5th percentile
  - Is a major cause of neonatal and maternal morbidity/mortality
  - There is no evidence-based treatment
  - In a majority of cases, vascular placental insufficiency might be involved
- **Sildenafil**
  - Is a potent and selective inhibitor of type 5 phosphodiesterase causing GMPc mediated arterial vasodilatation
  - It can improve uteroplacental flow by potentiating oestrogen induced vasodilation

Objectives

- To review the literature on the use of sildenafil in IUGR
- To describe the use of sildenafil in pregnant women with severe early-onset IUGR in our institution

Methods

- **Literature review**: Pubmed/EMBAse researche. Mesh terms used "intrauterine growth restriction" and "sildenafil". Inclusion : French and English writting articles up to January 2016 . Exclusion: studies using sildenafil for other indications than IUGR.
- **Case-series**: hospitalized pregnant women with known pregnancy outcomes who received sildenafil for severe IUGR at the CHU Sainte-Justine from January 2012 to November 2015. Patients were identified using the Pharmacy software program (Chartmaxx or paper). A standardized data collection sheet for all demographic, biological, pharmaceutical and clinical data was developed.

Results

Table 1: Review of medical literature

Study design (authors)	Subjects	Dose	Outcomes and conclusion
In vitro studies (Wareing et al. 2005, 2006)	27 normal pregnancies, 12 IUGR	Unknown	Significantly ↓vasoconstriction and improved relaxation of myometrial small arteries from pregnancies with IUGR.
Case report (Lin et al. 2012)	30 yo, G3P0, 26 weeks, IUGR <5th percentile, absence umbilical blood flow	25 mg 3x/day	↓ in uterine arteries pulsatility, resolution of uterine artery notch and ↑ in estimated fetal weight. No neonatal adverse events.
Case report (Panda et al. 2014)	32 yo, G4P0A3, 26+6weeks, absent umbilical artery end diastolic flow with cerebral dilatation	50 mg 2x/day increased gradually to 50 mg 3x/day	Improved uteroplacental flow. Delay of birth by 3 weeks. Mother and child were well at 1 month after birth.
Open-label pilot study (Von Dadelszen et al. 2011)	10 sildenafil, 17 sildenafil-naïve pregnancies at < 25 weeks	25 mg 3x/day	↑ in the growth velocity (using abdominal AC). Trend towards higher survival at discharge. Well tolerated.
Randomized controlled study (Dastjerdi et al. 2012)	29 Sildenafil, 30 placebo IUGR at 24-37 weeks	50 mg once daily	Trend to improvement of foetoplacental perfusion Headache (1 sildenafil/2 placebo) Flushing (1 placebo). Exclusions: anomalies, use of vasodilators, CV diseases, diastolic blood pressure > 110 mmHg and BMI > 34 kg/m^2

Table 2. Demographics before sildenafil

Maternal characteristics (n=19)	Results
Maternal age (years), median, [min, max]	31, [19, 39]
Ethnicity, n (%)	
Caucasian	13 (68)
Black	4 (21)
Asian	1 (5)
Hispanic	1 (5)
Maternal weignt (kg), median, [min, max]	71.4 [44.8, 123]
Maternal BMI (kg/m^2), n = 9, median, [min, max]	24.2, [24, 40]
Comorbidities, n (%)	
Diabetes (type 1, 2 or gestational)	5 (26)
Hypertension (chronic or gestational)	10 (53)
Dyslipidemia	1 (5)
APLS	1 (5)
Sickle cell anemia	1 (5)
IUGR history, n (%)	**6 (32)**
Pre-eclampsia history, n (%)	5 (26)
Previous premature delivery, n (%)	10 (53)
Nulliparous, n (%)	7 (37)
Pregnancy characteristics	
GA, weeks and days since LMP, median, [min, max]	25, [20+1, 30+6]
Uterine artery notching, n (%)	18 (95)
AC < 5thpercentile, n (%)	15 (79)
EFW (g), median, [min, max]	558, [237, 1208]
Umbilical artery Doppler absent/reversed flow, n (%)	8 (42)

- Average dosage of sildenafil: 20 mg orally 3x/day until delivery
- Start of treatment-to-delivery interval was 17 days (median)
  - Beta blockers continued after IUGR diagnosis: 4 (21%)
  - Beta blockers D/C after IUGR diagnosis: 1 (5%)

Table 3. Outcomes after use of sildenafil

Pregnancy complications	Results
Pre-eclampsia, n (%)	**14 (74)**
Severe hypertension, n (%)	11 (58)
Proteinuria, n (%)	8 (42)
HELLP, n (%)	4 (21)
Placenta praevia, n (%)	1 (5)
Severe oligohydramnios, n (%)	**1 (5)**
No significant weight gain for more than 2 weeks, n (%)	**2 (11)**
Umbilical artery Doppler reversed flow, n (%)	**4 (21)**
Fetal/neonatal outcomes	
Admission-to-delivery interval (days), median, [min, max]	**17, [5, 47]**
GA at delivery, weeks and days since LMP, median, [min-max]	**28+6, [24+2, 33]**
Birth weight at delivery (g), median, [min, max]	**807, [320, 1360]**
Live birth, n (%)	**17 (89)**
Survival at hospital discharge, n (%)	**15 (79)**

Legend: AC: Abdominal circumference, APLS: Antiphospholipid antibody syndrome, BMI: Body mass index, EFW: Estimated fetal weight, GA: Gestational age, HELLP: Hemolysis, Elevated Liver enzymes and Low Platelet count, LMP: Last menstrual period

- A majority of women developed pre-eclampsia
- Uteroplacental blood flow might have been improved by sildenafil
  - 8/19 had an absent or reversed umbilical flow before sildenafil
  - 5/8 of these pregnancies had a positive flow after
- Ratio of observed to expected AC growth was improved in 4 / 14 (29%) pregnancies
- 79% of the babies survived to hospital discharge
  - Of those who did not survive, two were stillborn , one died in six days of life of a suspected metabolic disease and one died of neonatal sepsis 3 weeks of life.
- No major adverse effects were reported by mothers

Discussion

- The results observed in our case series is similar to what we found in other publications.

Strenghts

- Described the clinical practice in a tertiary university center.
- Data collection was standardized and thorough since we included every hospitalized pregnant woman that took sildenafil for IUGR.

Limits

- Small sample and no control group
- Women who started sildenafil as outpatients were not included,
- Missing data to allow complete analysis of the results (EFW, Doppler, AC).
- No follow-up after babies' discharge

Conclusion

- Sildenafil may offer a new option to improve perinatal outcomes for women whose pregnancies are complicated by severe IUGR.
- A randomised controlled study will be able to determine if sildenafil improves outcomes.
- CHU Sainte-Justine was selected to participate to STRIDER protocol: a pilot trial planned to be started in 2016.

References

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Contact: ema.ferreira@umontreal.ca **Conflict of interest**: None **Funding**: None