



## **Risk of Intrauterine Growth Restriction Among Infants With and Without Congenital Cytomegalovirus (CMV) Infection**

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## What's is known about intrauterine growth restriction (IUGR) and congenital CMV infection (cCMV):

- **IUGR has been described in majority of infants with symptomatic cCMV**
- **Several maternal, placental, and fetal factors can lead to IUGR**
- **Infants with IUGR alone are not considered as symptomatic cCMV**



## **What questions need to be answered about IUGR and cCMV :**

- Is there an increased prevalence of cCMV in infants with IUGR compared to general population?**
- What is the prevalence of IUGR in asymptomatic infants from screened populations for cCMV?**

**This knowledge may contribute to evaluate a potential target CMV screening in this subgroup of infants.**

## **OBJECTIVES:**

- **Describe the prevalence of intrauterine growth restriction (IUGR) among infants from population screened for congenital CMV infection (cCMV)**
- **Evaluate the association between IUGR and cCMV**
- **Describe the fraction of severe IUGR in the population that is attributable to cCMV**

## Study design:



- **“Brazilian Cytomegalovirus Hearing and Maternal Secondary Infection Study” (BraCHS)**
- **Prospective study from September 2013 to April 2016**
- **A total of 11,784 singleton live-born infants screened for congenital CMV infection were included.**
- **Multiple births were excluded.**
- **The study was carried out at two public maternities at Ribeirão Preto city, state of São Paulo, Brazil.**
- **Approved by the Research Ethics Committee of the University Hospital (Process number 16.928/2013), and written informed consent was obtained from all participants.**

## **Study design:**

### **Congenital CMV screening and diagnosis:**

- **Congenital CMV infection was screened by CMV-DNA screening in two saliva swabs specimens ( right and left side of mouth) from each infant obtained in the first 2 weeks using a qualitative DNA-PCR assay.**
- **Positive saliva results were confirmed by testing second saliva and urine collected within 3 weeks from birth using a quantitative real time DNA-PCR assay.**
- **Diagnosis of congenital CMV infection was defined in infants with CMV-DNA detection in at least two saliva and one urine samples obtained before day 21.**

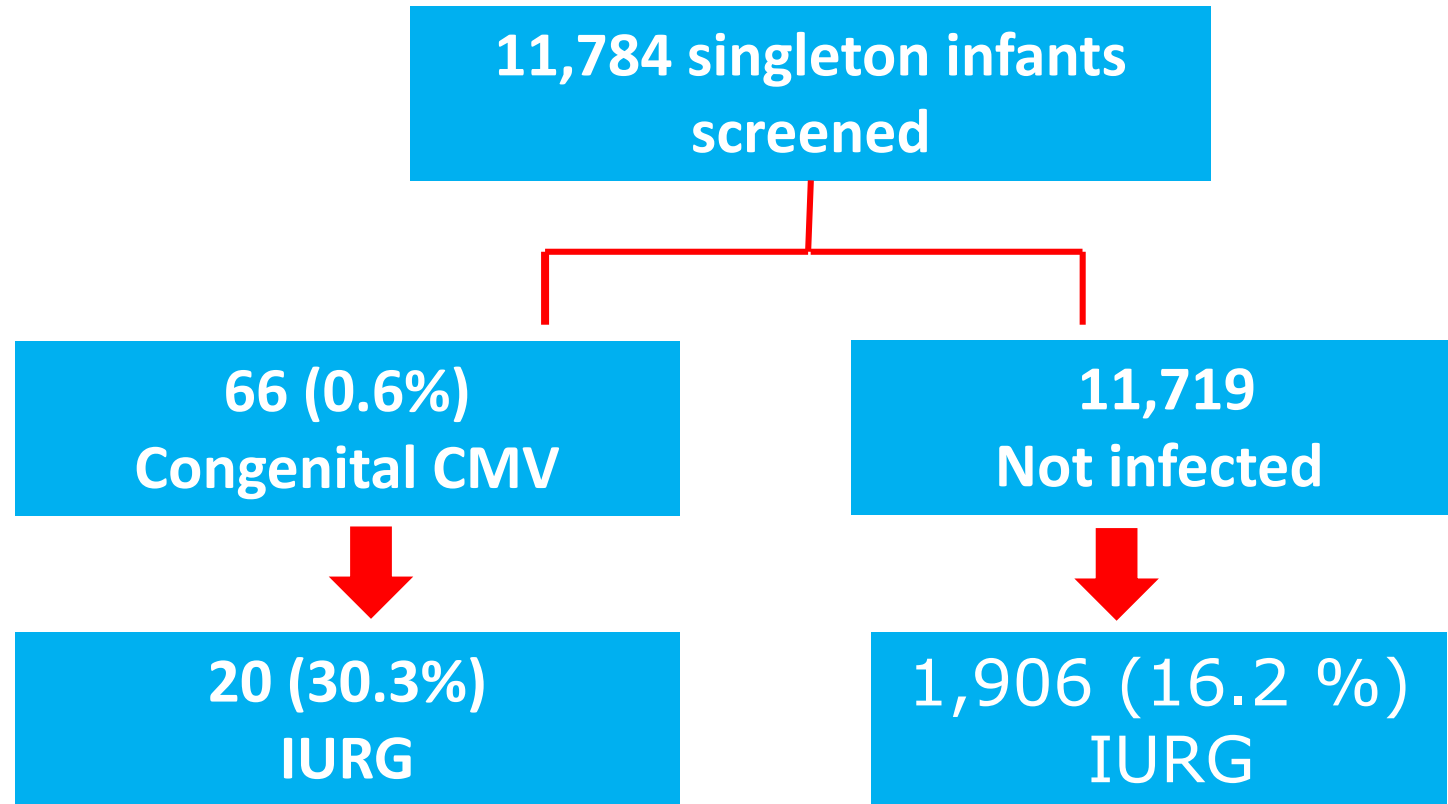
### **Definition of symptomatic cCMV infection:**

**Consensus recommendations, 2017, Lancet Infect Dis 2017; 17: e177–88**

## Methods: Study design

- ❑ Classification of birth weight for gestational age was based on Williams curve (*William RL et al. Obstet Gynecol 1982; 59(5): 624-32*).
  - ❑ Birth weight ratio (BWR): infant's birth weight compared to the mean reference birth weight for gestational age and gender
  - ❑ Intrauterine growth restricted : (*Kramer MS et al. Pediatrics 1989, 84:717-723*).
    - Mild : 0.80 to < 0.85
    - Moderate : 0.75 to < 0.80
    - Severe: <0.75 or 2.3 rd percentile.
- ❑ Gestational age :
  - First day of the last normal menstrual period and confirmed by early ultrasound.
  - If the difference was more than 7 days, the ultrasound gestational age estimate was used.

# Results:



**RR: 1.89; 95%CI: 1.35-3.89**

**Prevalence of cCMV among infants with and without IURG:  
(20/1,926 ; 1.03%) versus ( 45/ 11,764 ; 0.45%) ; p= 0.001**



## RESULTS: Association between maternal factors and IUGR

	IURG (RR; 95% CI)	No restriction
<b>Maternal age:</b>	<b>1.16 (1.01 ; 1.32)</b>	
• ≥18 years	1,731 (90%)	9,008 (91.4%)
• < 18 years	195 (10%)	850 (8.6%)
<b>Parity:</b>	<b>1.24 (1.14 ; 1.34)</b>	
• Primiparous	830 (43 %)	3,640 (36.9 %)
• ≥ 2	1,095 (57 %)	6,218 (63.1 %)
<b>Marital status:</b>	<b>1.14 (1,05 ; 1.24)</b>	
• Single	704 (36.5 %)	3,243 (32.9 %)
• Married	1,222 (63.5 %)	6,615 (67.1 %)
<b>Maternal schooling:</b>	<b>1.27 (1.16 ; 1.41)</b>	
≥ 9 years	1,501 (77.9 %)	8,143 (82.6 %)
< 9 years	425 (22.1 %)	1,714 (17.4 %)
<b>Prenatal care:</b>	<b>1.39 (1.27- 1.53)</b>	
≥ 7 visits	1406 (73.1 %)	7910 (80.3 %)
< 7 visits	518 (26.9 %)	1942(19.7 %)

# Results:

## Association between IUGR and cCMV after adjusting for maternal factors

	IUGR	No restriction
cCMV		
No	1,906	9,813 (83.7%)
Yes	20	45(69.2%)
Risk Ratio (RR) (CI 95%)	1.89 (1.31 ; 2.73)	
Risk Ratio (RR) after adjust *(CI 95%)	1.82 (1.26 ; 2.62)	

\* Maternal age, parity, marital status, maternal schooling, prenatal care.

## Results:

	IUGR			NO RESTRICTION
	Severe	Moderate	Mild	
cCMV				
No	536 (4.6 %)	495 (4.2 %)	875 (7.5 %)	9,813 (83.7 %)
Yes	10 (15.4 %)	6(9.2 %)	4(6.1 %)	45(69.2 %)
	RR (Severe)	RR (Moderate)	RR (Mild)	
Risk Ratio (RR) (CI 95%)	3.36 (1.89; 5.98)	2.18 (1.01; 4.71)	0.82 (0.31; 2.13)	

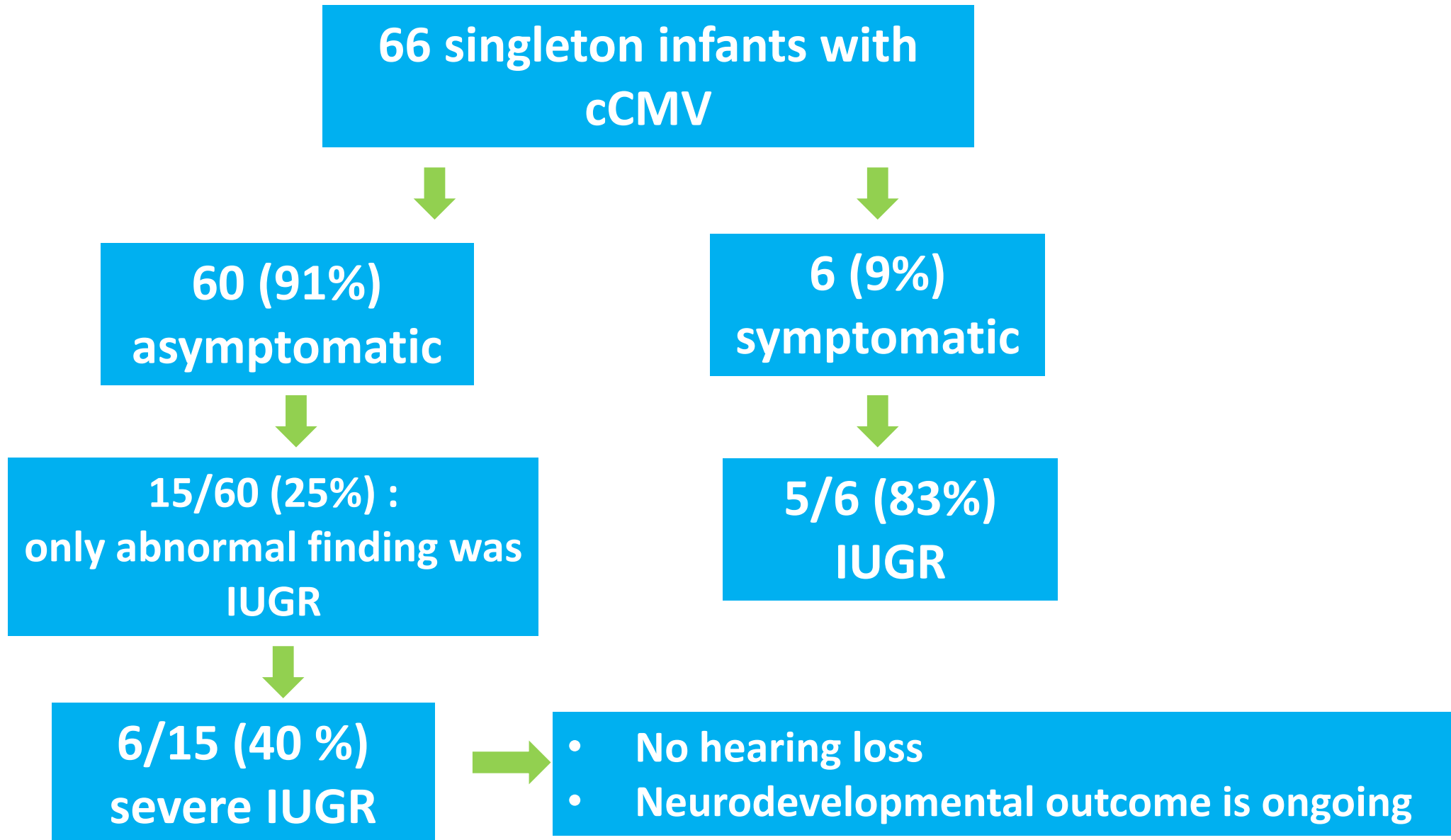
# Results:

## Fraction of IUGR in the population attributable to cCMV

	Severe	Moderate/ Severe	Mild to Severe
	Value (IC95%)	Value (IC95%)	Value (IC95%)
Risk in exposed (cCMV)	15.38% (8.37 ; 26.25%)	24.62% (15.67 ; 36.4%)	30.77% (20.84 ; 42.85%)
Risk in unexposed (without cCMV)	4.57% (4.21 ; 4.97%)	8.80% (8.29 ; 9.32%)	16.26% (15.61 ; 16.94%)
Risk Ratio	3.36 (1.89 ; 5.98)	2.79 (1.82 ; 4.29)	1.89 (1.31 ; 2.73)
Etiologic fraction in pop (Efp)	1.29% (0.20 - 2.73%)	0.98% (0.29-1.67%)	0.49% (0.09-0.88%)

# Results:

## Characteristics of infants with IUGR and cCMV



## Summary and data from other published studies:

Study	Study population	Congenital CMV	IURG in infants with and without cCMV	cCMV in infants with and without IURG
Present study	11,784 singleton infants screened for cCMV	65 (0.6 %) 6 symptomatic (9%)	20/65 ( <u>30.8%</u> ) versus 1,906/ 11,784 ( <u>16.2%</u> )	20/1,926 ( <u>1.04%</u> ) versus 45/11,764 ( <u>0.4%</u> )
Wang S. et al., 2017	10,933 infants screened for cCMV	75 (0.7%) No symptomatic	5/75 ( <u>6.6%</u> ) versus 280/10,858 ( <u>2.6 %</u> )	5/285 ( <u>1.8%</u> ) versus 70/10,647 ( <u>0.7%</u> ) p= 0.03

## Conclusions:

- **About a third of CMV-infected infants had IUGR.**
- **IUGR was the only abnormal finding in one-fourth of CMV-infected infants.**
- **Infants with cCMV were at significantly increased risk for IUGR compared to uninfected infants.**
- **These results support consideration of CMV testing of infants with IUGR.**

# Acknowledgements



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All study  
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