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A pilot study on peak systolic velocity monitoring of fetal anemia after administration of chemotherapy during pregnancy

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ABSTRACT

Objectives: To monitor fetal anemia during administration of chemotherapy to the fetus's mother.
Study design: Between 2007 and 2012 six patients with malignancy diagnosed during pregnancy were included in our prospective study. For evaluation of fetal anemia, peak systolic velocimetry (PSV) of the middle cerebral artery is considered the best method. The patients were repeatedly examined one day before and on the third day after the administration of chemotherapy. At least three measurements were performed and the highest value was used as appropriate. Multiples of the median (MoM) were calculated using the website http://www.perinatology.com/calculators/MCA.htm. When the MoM reached 1.29, moderate anemia was diagnosed.
Results: The women's average age was 30 years. The average gestational age at diagnosis was 20.7 weeks of pregnancy. Borderline fetal anemia was detected in only in one patient. After delivery newborns were examined by standard pediatric evaluation and blood count was provided. There was no evidence of any newborn anemia.
Conclusions: Chemotherapy administered during pregnancy is becoming more frequent due to increasing knowledge and data on such cases. Close monitoring of the fetus should be performed in specialized centers. For detection of chemotherapy-induced anemia, PSV measurement should be employed.

1. Introduction

The average age of women at delivery is increasing as women nowadays tend to postpone their childbearing plans. The diagnosis of malignant disease during pregnancy is therefore becoming more frequent. One of the treatment modalities used during pregnancy is chemotherapy, which has been intensively studied in recent years [1]. The influence of chemotherapy on adults is well described for each regimen. Among other side effects, granulocytopenia occurs between 6 and 12 days and thrombocytopenia from 10 to 17 days after chemotherapy. Standard examinations during chemotherapy include blood count, biochemistry tests and creatinine clearance. Intrauterine monitoring of the fetus is far more difficult.

Fetal anemia and thrombocytopenia may arise from immune and non-immune causes. One of the etiopathological mechanisms is chemotherapy applied during pregnancy, especially when platinum derivatives are used [2]. Umbilical cord sampling for evaluation of fetal blood count and blood transfusion is standard management for fetal anemia, but for routine use it is too invasive [3]. With advancements in Doppler velocimetry, ultrasound examination has become a unique non-invasive method to evaluate the side effects of chemotherapy. Studies on animal models have shown that the velocity of fetal blood flow increases with increased cardiac output and reduced blood viscosity [4]. The most sensitive metric appears to be the peak systolic velocity (PSV) measured in the middle cerebral artery (MCA) [5–7]. Various other measures have been tested to predict fetal anemia, for example umbilical cord diameter measures [8], placental thickness [9], liver length [10] and spleen circumference [11], but velocimetry of the MCA has been found superior to other methods in predicting fetal anemia [12].

Mari et al. established nomogram curves based on multiples of the median (MoM) for hemoglobin levels and PSV of the MCA from 18 to 40 weeks of gestation [13]. Today, a cut-off of 1.29 MoM for gestational age indicates moderate fetal anemia, and 1.5 severe fetal anemia. These can indicate when further invasive investigation of fetal levels of hemoglobin and hematocrit is required. After intrauterine transfusion (IUT), the sensitivity and specificity of the examination decreases, probably because of rheological changes

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Table 1
Demographic, clinical and perinatal data.

		Patient	KD	DD	TS	LR	PM	MK
Patient		Age	30	36	26	36	21	31
		Gravidity	2	1	1	1	1	2
		Parity	2	1	1	1	1	2
		Diagnosis	Ovarian ca.	Ovarian ca.	Breast ca.	Ovarian ca.	Cervical ca.	Cervical ca.
		Histological type	Endometroid	Clear cell	Ductal	Clear cell	Squamous	Adeno
		Stage	IC	IC	II	IC	IB1	IB1
		GA at diagnosis	15	16	23	18	27	25
		Chemotherapy	6 × P	6 × TP	3 × FAC, 1 × T	4 × T + CBDCA	3 × TP	4 × PA
		GA at last chemotherapy	32 + 3	31 + 5	31 + 4	29 + 5	33 + 1	31 + 4
		Delivery (week)	36 + 5	35 + 5	35 + 6	37 + 2	37 + 0	34 + 6
		Type of delivery	Cesarean section	Cesarean section	Cesarean section	Spontaneous	Cesarean section	Cesarean section
	Blood count before delivery	Leu ($\times 10^9$/l)	6.8	9.2	8	9.1	12.5	8.3
		Hct	0.328	0.282	0.345	0.318	0.336	0.294
		Hgb (g/dl)	11.1	9.6	11.2	11.2	11.2	10.1
		Plt ($\times 10^9$/l)	145	187	218	135	292	199
New born		Sex	Female	Female	Male	Male	Female	Female
		Birth weight (g)	2720	1930	2600	2710	3250	2420
		Birth height (cm)	46	44	44	50	49	NA
		Head circumference	32	30	33	33	31	34
		Apgar score	10/10/10	7/8/9	9/10/10	9/10/10	9/10/10	9/10/10
		pHartery/BE	7.28/−2.7	7167/−7.0	7243/−4.0	7.27/−3.0	7246/−5.0	7243/−5.2
		pHvein/BE	7.33/−3.3	7233/−4.9	7255/−3.2	7301/−2.2	7354/−1.9	7360/−2.4
	Blood count	Leu ($\times 10^9$/l)	10.3	13.5	15.5	4.5	17.5	11.2
		Hct	0.421	0.463	0.51	0.397	0.411	0.361
		Hgb (g/dl)	14	16.1	18.1	13.3	14.3	12.4
		Plt ($\times 10^9$/l)	334	335	326	223	275	287
		Child at delivery	Normal	Normal	Hyper-bilirubinemia	Hyper-bilirubinemia	Normal	Normal
		Follow-up child (months)	56	55	52	49	36	23
		Child at follow-up	Normal	Central neurologic hypotony, microcephaly	Normal	Normal	Normal	Normal

GA, gestational age; P, cisplatin (75 mg/m^2); T, paclitaxel (175 mg/m^2); F, fluoruracil (500 mg/m^2); A, doxorubicin (50 mg/m^2); C, cyclophosphamide (500 mg/m^2); CBDCA, carboplatin (5AUC); AUC, area under the curve; Leu, leucocytes; Hct, hematocrit; Hgb, hemoglobin; Plt, platelets; BE, base excess; NA, not applicable.

caused by adult donor blood cells present in the circulation [14]. The PSV measurement has been also used in the detection of fetomaternal hemorrhage in a patient with metastatic gestational choriocarcinoma [15].

The aim of our study was to monitor anemia of the fetus during administration of chemotherapy to the fetus's mother.

2. Materials and methods

Between 2007 and 2012, six patients with malignancy diagnosed during pregnancy were included in our prospective study. Informed consent, approved by the ethical committee of the 2nd Faculty of Medicine of Charles University in Prague, was obtained from all study participants. The patients were examined one day before chemotherapy and on the third day after chemotherapy. Ultrasonographic examination was performed by one of three examiners (M.J.H., M.K., R.V.) using a Toshiba Xario ultrasound machine with a 5 MHz probe. The Doppler measurement was performed in a transverse plane and the MCA vessel was located by color Doppler imaging near the base of the skull. The insonation of the ultrasound beam was at an angle of 0° to the branch of the artery closest to the transducer. A sample volume of 1–2 mm was placed along the vessel just after bifurcation from the carotid artery. Obtained waveforms should be relatively uniform. At least three measurements were performed and the highest value was used as appropriate. Electronic tracing was used for determination of the curve. The website http://www.perinatology.com/calculators/MCA.htm was used to calculate the MoM. Moderate and severe anemia was diagnosed at MoM levels 1.29 and 1.5 respectively.

3. Results

Characteristics, diagnosis, chemotherapy and blood count of patients and newborns are presented in Table 1. The patients' average age was 30 years. The average gestational age at diagnosis was 20 + 5 weeks of pregnancy. Altogether, 24 examinations were performed (four per patient on average). Fig. 1 displays the results of measurements of PSV and MoM. In only one patient (MK) was borderline anemia detected. After delivery, all newborns were examined by standard pediatric evaluation and blood count was provided. There was no evidence of any newborn anemia.

4. Comments

To our knowledge, this is the first prospective study to follow fetuses exposed to chemotherapy in utero in relation to anemia at exactly chosen time points. Until now only one conference presentation [16] and one publication [17] reported the potential of PSV measurement in detection of fetal anemia induced by chemotherapy.

If hemoglobin values drop to 6–7 SD below the mean for gestational age, hydrops fetalis can occur, unfortunately as a late stage of fetal anemia. Therefore, fetuses at risk of fetal anemia (such as those exposed to chemotherapy in utero) should be screened for an increase in peak velocities of the MCA. Various possibilities are available if fetal anemia is detected. In moderate anemia, a delay in chemotherapy could be considered if close follow-up of the Doppler parameters is initiated. An excessive delay (over one week) could, on the other hand, compromise the effectiveness of the oncologic treatment. In prolonged anemia or