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Pregnancy in women with osteogenesis imperfecta: Pregnancy characteristics, maternal, and neonatal outcomes

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Abstract

Background: Women with rare diseases such as osteogenesis imperfecta may consider pregnancy, although data regarding outcomes, specific risks, and management strategies is lacking.

Objective: The Brittle Bone Disorders Consortium of the National Institute of Health Rare Diseases Clinical Research Network established an Osteogenesis Imperfecta Pregnancy Registry to collect and evaluate pregnancy, maternal, and neonatal outcomes in women with osteogenesis imperfecta

Study Design: This is a cross-sectional, survey-based study. Appropriate participants of the Brittle Bone Disorders Consortium Contact Registry were invited to participate in the study. Self-reported information regarding pregnancy characteristics and maternal and neonatal outcomes was compared to the general population, referenced by literature-based standards, and comparisons between cohorts of women and fetuses with osteogenesis imperfecta were evaluated to determine if the presence of osteogenesis imperfecta conveyed an increase in antepartum, intrapartum, and postpartum complications and an increase in adverse neonatal outcomes when compared to the general population.

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Results: 132 Participants completed the survey. Compared to the general population, women with osteogenesis imperfecta had higher rates of diabetes in pregnancy (13.3% vs. 7%, p=0.049, CI: 7.0%−19.6%), cesarean section (68.5% vs. 32.7%, p<0.001, CI: 59.9–77.1%), need for blood transfusion (8.3% vs. 1.5%, p=0.019, CI: 3.9–12.8%), and antepartum and postpartum fractures (RR 221, 95% CI: 59.3–823, p<0.001). Maternal hospitalization and cesarean rates were higher in individuals with moderate or severe osteogenesis imperfecta as compared to the women who reported mild osteogenesis imperfecta. Neonates born to women with osteogenesis imperfecta had higher risk for being low (26.2% vs. 6.8%, p<0.001) or very low birth weight (13.8% vs. 1.4%, p<0.001) infants as compared to the general population. Neonates born to women with osteogenesis imperfecta had a higher rate of neonatal intensive care unit admissions (19% vs. 5.68%, p<0.001) and higher neonatal mortality at 28 days of life (4.8% vs. 0.4%, p=0.026), regardless of neonatal osteogenesis imperfecta status.

Conclusion: Pregnancies for women with osteogenesis imperfecta are at an increased risk for complications including hemorrhage, fractures, diabetes, and increased neonatal morbidity.

Condensation:

Women with osteogenesis imperfecta are at an increased risk for pregnancy complications including hemorrhage, fractures, diabetes, and increased neonatal morbidity and mortality.

Keywords

Osteogenesis Imperfecta; pregnancy; fractures; maternal; neonatal outcomes

Introduction:

In the United States, a rare disease is defined as a disorder that affects less than 200,000 individuals [1]. Osteogenesis imperfecta (OI), also known as brittle bone disease, is a prototype rare disease and with therapeutic advances, more individuals with these disorders are reaching reproductive age. While guidelines for pregnancy management in the general population are well established, there are limited data regarding pregnancy management in women with OI. Now that therapies such as bisphosphonates have improved the overall quality of life by decreasing fracture incidence and for some individuals, improved survival [2]more women with OI reach adulthood, and pregnancy with its concomitant risks becomes a concern to both patients and treating physicians.

OI is a genetically heterogeneous connective tissue disorder that affects an estimated 6 to 7 per 100,000 individuals worldwide and has a birth prevalence of 0.3 to 0.7 per 10,000 [3]. More than 80% of cases are caused by pathogenic variants in two genes that encode type I collagen, *COL1A1* and *COL1A2* [4,5] and genomic advances have identified 18 additional genes as causes for OI [6]. The musculoskeletal system is primarily affected in OI and thus primary manifestations include low bone mass and bone fragility that lead to recurrent appendicular and axial skeletal fractures and variable bone deformities[5,7]. While OI is a generalized connective tissue disorder, and other complications include hearing loss, dentinogenesis imperfecta, pulmonary dysfunction, cardiac valvular abnormalities, short stature, and pain [5,8–10]. OI is clinically complex and the most clinically utilized

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classification groups individuals into types I, II, III and IV correlating to the phenotypic range of mild, lethal, severe progressive deforming, and moderate, respectively [11]. This Sillence classification does not reflect the true genetic heterogeneity of the syndrome and with advances in molecular investigations, there are now 20 distinct forms of OI[12]; however, it remains useful in terms of genetic counseling and for the prediction of the clinical evolution of this disorder.

Given the notable physiologic changes that occur during pregnancy, the question is whether pregnancies in women with OI convey additional risks based on OI associated physiology. Retrospective cohorts, case reports, and small case series describe increased rates of cesarean sections, breech presentation, and preterm birth [13–18]. To date, one cross sectional study used a questionnaire format investigating pregnancy and delivery characteristics in women with OI [15]. While the aforementioned studies have contributed, significant gaps remain in understanding pregnancy associated risks and complications. The Brittle Bone Disorders Consortium (BBDC) which is part of the Rare Diseases Clinical Research Network (RDCRN) of the National Institutes of Health, designed a Pregnancy in Osteogenesis Imperfecta Registry to determine the maternal characteristics in OI, course of pregnancy, and outcomes of pregnancies in order to improve counseling and provide anticipatory guidance to patients.

Materials and Methods

This was a cross-sectional, survey-based study. The University of South Florida Institutional Review Board granted approval for this study and it was enrolled in ClinicalTrials.gov: NCT03072303. Implementation of the survey, data collection, and analysis were coordinated by the RDCRN's Data Management Coordination Center (DMCC). The RDCRN using the BBDC Contact Registry invited eligible participants via email to participate in this study from May 2017 until January 2018.

Inclusion criteria were as follows: women with OI who had delivered a child (defined as a birth >20 weeks gestational age). Participants with the following characteristics were excluded from the study: 1) inability to provide informed consent and complete the survey, and 2) women with OI and higher order multiples.

The BBDC Contact Registry sent two separate e-mail blasts to introduce and complete the pregnancy survey. Once registered, informed consent was obtained, participants were informed of the survey procedural and security details, and participants were given access to the online questionnaires. Participants entered the data directly online, using encrypted communication links. All study data were collected anonymously (de-identified) and analyzed via systems created in collaboration between the RDCRN DMCC and the BBDC.

The primary maternal, delivery, and neonatal outcomes included rates for: preterm birth, cesarean section, regional anesthesia, diabetes and hypertension during pregnancy, NICU admission, birth weight, congenital defects, gestational age at delivery, transfusion incidence, and antepartum and postpartum fractures. The secondary outcome measures included: abortion rate, assisted reproductive technology use, weight gain in pregnancy,

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proportion who exercised during pregnancy, and rate of breastfeeding. Additionally, data on maternal mobility, hospitalization during pregnancy, and medication use were also collected.

The minimum expected number of participants at the start of the study was 100. The proportions of individuals in the study population with each of the primary and secondary outcomes and their 95% confidence intervals were calculated using standard techniques. The observed proportions (for ordinal data) and average values (for continuous data) in women with OI were compared with established and accepted normative data from the literature on these outcomes in the general population using the one-sample proportion test and the one sample t-test, respectively. Weighted analysis was performed for the measured outcomes, to account for participants entering data on multiple, consecutive pregnancies. Descriptive outcomes were reported using proportions, means, or medians with ranges. Differences in the characteristics between women with mild vs moderately severe OI, presence or absence of an OI affected fetus, and incidence of fractures were tested using t-test or ANOVA for continuous outcomes, and the Fisher's exact test or the chi-square test as appropriate. An alpha error value of less than 0.05 was considered as statistically significant.

Results:

The BBDC Registry has a total of approximately 1,600 members and they self-identify their type of OI or phenotypic severity. A total of 170 members were considered eligible based on inclusion criteria and initially registered for the study. 132 eligible participants completed the survey: survey response rate = 77.6%. While there were a total of 132 participants, this study was designed to be able to assess each pregnancy episode; thus, individuals with multiple pregnancies could report on each one. At the study closure, data were collected on a total of 170 pregnancies. The response rates for each characteristic queried on the survey was variable; thus, analysis was calculated based on the total number of responses for each characteristic.

Demographic data for survey participants is listed in Table I. In contrast to 2013 CDC data demonstrating that Caucasian women comprised 54% of deliveries in the United States, in our study cohort the majority self-identified as Caucasian (97.7%) [19]. Pregnant women with OI were of smaller stature (154.9 cm) compared to the average non-Hispanic white American (163 cm) and had a lower BMI (26.7 vs. 29 kg/m^2) [20]. The median number of living children per respondent was 2, 74.4% self-reported as having mild OI, and 96.9% reported none or minimal limitations with mobility. Although the precise period of bisphosphonate medication exposure could not be determined, 6 out of 167 (3.6%) respondents noted bisphosphonate during or up to the period leading up to pregnancy. Regarding their partner's health, only 2/168 (1%) respondents reported that their partner also had OI.

Maternal and neonatal outcomes are described in Table II. Compared to normative data, women with OI reported higher rates of assisted reproductive technology use (6.9% vs. 1.5%, p=0.035, CI: 1.9%−12.0%), diabetes (13.3% vs. 7%, p=0.049, CI: 7.0%−19.6%), cesarean section (68.5% vs. 32.7%, p<0.001, CI: 59.9–77.1%), breech presentation (12.6 vs. 4%, p=0.007, CI: 6.41%−18.84%), and blood transfusion (8.3% vs. 1.5%, p=0.019, CI:

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3.9–12.8%) [19,21–23]. Women with OI had lower rates of regional anesthesia use during labor (28.5 vs. 61%, p<0.001, CI: 20.3% - 36.7%), but had similar rates of back pain, exercise, hypertension, depression, preterm labor, and breastfeeding at 1 month post-delivery [24–28]. While women with OI are statistically less likely to deliver at 40 weeks (Table II), duration of pregnancy was not associated with disease subtype. Compared to normative data, women with OI lower elective abortion (4% vs. 21%, p<0.001, CI: 1.9%−6.2%)[29] and breastfeeding rates at 6 months (34.8% vs. 51.4%, p<0.001, CI 26.0%−43.6%)[28].

Neonatal outcomes are presented in Table III. Women with OI delivered neonates with an average birth weight of 2722 g. Notably, respondents delivered a higher proportion of neonates with low birth weight, i.e., <2500gm (26.2% vs. 6.8%, p<0.001, CI: 18.7% −33.7%) and very low birth weight, i.e., <1500gm (13.8% vs. 1.4%, p<0.001, CI: 7.7% −20.0%) [30]. Newborns had higher rates of admissions to the neonatal intensive care unit compared to the general population (19% vs. 5.68%, p<0.001, CI: 11.9%−26.0%) [19]. Although the overall rate of survival past 28 days was 95%, 8 neonates (4.8%) did not survive beyond 28 days. This neonatal mortality rate is higher compared to normative data (4.8% vs. 0.4%, p=0.026, CI: 0.9%−8.2%)[19]. Eighty-one respondents (48.5%) reported that their child had OI and there were 8 (4.8%) infants with other congenital birth defects including cleft lip/palate (1.2%), congenital heart anomalies (1.2%), spina bifida (1.2%), clubfoot (0.6%), and unclassified others (1.2%).

Table IV [A, B, C] details pregnancy and delivery characteristics and complications. Characteristics specific to OI are included in Table IV-A. There were 17 (10%) reported fractures during pregnancy, of which feet or toes, forearm, and spine were the most common sites. There was a total of 20 (12%) fractures after pregnancy (defined as fractures occurring within 2 months after delivery), with the spine and ‘other bones’ designated as the most common sites. Compared to the general population rate of fracture in pregnancy of 0.029% [31], the relative risk of a fracture during pregnancy in OI was 221 (95% CI 59.3 – 823, p<0.001). Whereas in women self-identifying as having mild OI, the relative risk of fracture compared to the general population was 311 (95% CI 84.1 – 1153, p< 0.001), in women with moderate or severe OI, the relative risk was 903 (95% CI 224.4 – 3636.3, p<0.001). A total of 2.4% of all antepartum hospitalizations were specifically for bed rest secondary to OI. Although rates of back pain during pregnancy were similar (60%) when compared to the normative data (68.5%) [24], 75.5% reported that back pain worsened during pregnancy. Of those who reported worsening pain during pregnancy, 10.6% required medication for back pain in pregnancy and 43.6% reported that the pain limited activity or mobility.

Table V demonstrates comparisons of characteristics considered to be of special interest to pregnant women with OI. Outcomes were analyzed to ascertain if there were any specific differences in women with OI for the following: pregnancies complicated by the presence of fractures, the index pregnancy affected by a fetus with OI, and the severity of OI. Table V-A describes characteristics of women with OI who experienced fractures during pregnancy compared to women with OI who did not experience fractures during pregnancy. Interestingly, there were no differences in proportions of individuals with medications use, mobility level, exercise in pregnancy, or hospitalization during pregnancy.

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Table V-B demonstrates a comparison of characteristics and pregnancy outcomes when the fetus had OI compared to those pregnancies without fetal OI. The following differences were statistically significant: birth weights were lower in neonates with OI (2503 g vs. 2943 g, p=0.02). For those pregnancies in which the fetus had OI, the rate of vaginal delivery (33 vs. 20, p=0.04) was statistically higher compared to those where the fetus did not have OI. The rates of premature labor (17% vs. 14%, p= 0.66), cesarean section (60% vs. 73%, p= 0.08), and cephalic presentation (90% vs. 84%, p= 0.34) were not significantly different between these two groups. In addition, fetal OI status did not significantly affect NICU admission rates (17% vs. 16%, p= 0.77) or ability to survive at least 28 days after birth (95% vs. 96%, p= 1.00). There were no significant differences in mean rates of abortion (4.58 vs. 5.05, p= 0.87) between the two groups.

Table V-C demonstrates pregnancy characteristics and outcomes based on the self-reported severity of OI. Vaginal delivery rates were higher in the mild OI group (43.4%) and cesarean delivery rates higher in the moderate or severe OI group (89.2% p<0.001). Exercise rates were similar across OI types in the first and second trimesters; however, in the third trimester, proportion of individuals who exercised was higher in the mild OI group compared to the moderate/severe OI group (30.7% vs 10.8%, p=0.019). Mean weight gain during pregnancy was higher in the mild group (14.66kg vs. 8.66kg, p< 0.001). Hospitalizations during pregnancy occurred more frequently in the moderate or severe OI group (8.1% vs 0.8%, p=0.036). Bisphosphonate usage during pregnancy was noted for 6 respondents and not associated with OI severity. Similarly, fracture risk was not statistical different based on phenotypic severity. While the incidence of transfusions in OI pregnancies was significant (Table II), no difference was seen between the mild and moderate/severe OI groups.

Comment:

Principal Findings:

This is the first, large, registry-based survey reporting on a wide range of pregnancy characteristics in women with OI. This study demonstrates that pregnancies for women with osteogenesis imperfecta are at a statistically increased risk for complications including hemorrhage, fractures, diabetes, and increased neonatal morbidity and mortality.

Results:

Demographics of the study participants compared to the general population are, as expected, notable for shorter stature and a lower BMI. Not surprisingly the majority of respondents were affected with mild OI; they have few mobility limitations, are the largest group of individuals with OI [5,32] and are likely to have a successful pregnancy. Yet, 34% of our cohort had moderate to severe OI and this proportion is higher than previously reported [15,18], providing insights into this less studied subgroup. Our study also evaluated characteristics not previously reported. For example, only 2 women (1%) had a partner with OI. While this is higher than the 0.007% general population incidence of OI, it is a lower rate of non-assortative mating when compared to other genetic communities [33,34]. In addition, we

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describe that previously unreported breastfeeding rates in the immediate postpartum were similar to normative data but decreased at 6 months.

When compared to U.S. normative data, OI pregnancies had higher rates of malpresentation, cesarean delivery, and blood transfusions and are compatible with results from prior studies [13–15]. While fractures in pregnant women with OI have been previously alluded to [15,18], this study described and differentiated between rates of pregnancy and postpartum fractures and quantified the increased relative risk.

Regarding neonatal outcomes, in accordance with previously published data, our study demonstrates higher rates of low and very low birth weights in neonates born to women with OI. Additionally, this study reports that neonates born to women with OI have higher rates of NICU admissions and neonatal mortality past 28 days, regardless of the fetal OI status. The incidence of congenital birth defects (not including OI) was similar to normative data, which is in contrast to previously reported studies [13].

Clinical Implications:

There is a transient decrease in bone mineral density and increased rates of bone resorption during the third trimester and lactation [35] and with OI, fracture rates may potentially increase due to pregnancy-induced bone loss. This study describes a decrease in breastfeeding rates after pregnancy compared to normative data, yet it is unclear if prolonged lactation was discouraged to prevent fractures or if cessation occurred for other reasons. Further research is required to understand lactation and any possible association with fracture rate in this population.

Interestingly, there was no difference in fracture incidence among women based on OI severity. This suggests an inherently intrinsic risk regardless of whether OI is mild or more severe and is not only relevant in counseling all women with OI who desire pregnancy, but also opens up a critical question of how to address this serious complication in future studies.

When evaluating pregnancies where the fetus had OI, these fetuses were not significantly more likely to be in breech presentation or delivered by cesarean section when compared to fetuses without OI. In fact, pregnancies wherein the fetus had OI were more likely to be delivered vaginally. We have previously published that mode of delivery of OI fetuses does not affect the at-birth fracture rate (i.e., presence or absence of fracture) [17]. While rates of neonatal fracture were not evaluated in this study, the findings from this study and our prior study support that a mere prenatal diagnosis of fetal OI is not an indication for delivery by cesarean section. In addition, our study demonstrates that non-cephalic fetal presentation is not statistically different in fetuses with OI compared to those without OI. Lastly, in accordance with prior studies, women with mild OI were more likely to have a vaginal delivery compared to the moderate or severe OI group, likely due to higher rates of cephalopelvic disproportion associated with OI severity.

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Research Implications:

Further studies are needed to address whether fracture incidence can be decreased, whether the benefits of breastfeeding outweigh the risk to the maternal skeleton, and whether these women should be antenatally classified as high-risk for hemorrhage. Further research is necessary to establish practice recommendations that can optimize pregnancy and neonatal outcomes, and the long-term health of women with OI.

Strengths and Limitations:

This study is the most comprehensive report on the characteristics and outcomes among women with OI in pregnancy. Compiling and evaluating pregnancy information and outcomes in rare diseases is difficult, often without appropriate control groups. The strength of this survey data is in its ability to query an existing registry to gather pertinent information. While there are survey data limitations, such as difficulty generalizing conclusions received from personal recall and the dependence on memory, we believe that for the information we queried, there is likely to be limited discordance with actual data as women are unlikely to forget important details of their pregnancy and delivery. For example, mode of delivery (cesarean section vs. vaginal delivery), need for blood transfusion, neonatal death, and fractures are significant issues that are unlikely to be forgotten or confused with other clinical manifestations. We acknowledge that survey data self-reported by the participants may contain data-entry errors which may affect accuracy of results, but overall response rates were reasonable. Additional limitations, inherent to survey studies, are that the characteristics such as OI severity are self-reported by patients with no genetic/clinical evaluation for confirmation. In addition, although overall the response rates to this survey were high, rare individual response rates to certain questions: ie: bisphosphonate use in pregnancy, were low in which case generalizability for these responses may be difficult.

Conclusions:

We believe that the study methodology and data obtained via a Contact Registry represent a model for developing a comprehensive pregnancy database in women with rare diseases. The data supports that women with OI have successful pregnancies but are at increased risk for complications. Patients and providers should be aware of these findings, particularly the need for blood products (hemorrhage) and the increased rate of fractures, low birth weight infants, and neonatal mortality. Most importantly, serious sequalae occurred across the phenotypic spectrum of OI, including mildly affected individuals. This is particularly crucial for the increased incidence of transfusions, since maternal hemorrhage is the leading cause of maternal mortality [36]. Awareness of these complications can allow for adequate preconception counseling and proactive measures to reduce any potential harm and recognize modifiable risk factors related to pregnancy.

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AJOG at a Glance:

A. Why was the study conducted?

- **a.** Pregnancy information and management guidelines for women with rare diseases is lacking.
- **b.** The Osteogenesis Imperfecta Pregnancy Registry was established to collect and evaluate pregnancy, maternal, and neonatal outcomes in women with osteogenesis imperfecta.

B. What are the key findings?

- **a.** Pregnancies for women with osteogenesis imperfecta are at an increased risk for complications including hemorrhage, fractures, diabetes, and increased neonatal morbidity.

C. What does the study add to what is already known?

- **a.** Women with osteogenesis imperfecta have a 10–12% rate of fracture during pregnancy and the postpartum time period and an increased relative risk of fracture compared to the general population
- **b.** Neonates born to women with osteogenesis imperfecta have an increased rate of NICU admission and overall mortality at 28 days of life, regardless of neonatal osteogenesis imperfecta status.

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Table I:

Demographic characteristics of individuals with OI who responded to the survey

Characteristic	Value	Number of responses recorded for a characteristic
Median age, years [a]	42.5	122
Median height, cm (range) [a]	154.9 (106.7–177.8)	128
Median weight, kg (range) [a]	63.3 (35.4–129.3)	126
Median BMI (range) [a]	26.7 (17.7–41.2)	126
Ethnicity		132
Hispanic, Latino, or Spanish origin, %	1.5	2
Not Hispanic, Latino, or Spanish origin, %	86.4	114
Unknown or not reported in, %	12.1	16
Race		132
Black or African American, %	2.3	3
White, %	97.7	129
Self-identified severity of OI		129
Mild, %	74.4	96
Moderate, %	24	31
Severe, %	1.6	2
Exercise		168
Exercise prior to pregnancy, %	44	74
Weightlifting, %	8	14
High intensity interval, %	1	2
Running, %	6	10
Walking, %	33	56
Cycling, %	11	18
Elliptical, %	6	10
Hiking, %	2	4
Swimming, %	11	19
Dancing, %	2	4
Yoga/Pilates, %	6	10
Martial arts, %	0	0
High impact sports, %	<1	1
Other, %	2	3
Bisphosphonate taken during pregnancy or right until pregnancy		6
Yes, %	66.7	4
Mobility level		131
No restrictions, %	48.9	64
Some limitations, %	48	63

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Characteristic	Value	Number of responses recorded for a characteristic
Wheelchair dependent, %	3.1	4
Back pain prior to pregnancy		167
Yes, %	50	84
Number of miscarriages, median (range)	0 (0.0–4.0)	127
Number of therapeutic abortions, median (range)	0 (0.0–2.0)	127
Number of living children, median (range)	2.0 (0.0–6.0)	132
% with 0 children	0.8	1
% with 1 child	35.6	47
% with 2 children	38.6	51
% with 3 children	23.5	31
% with 4 children	0.8	1
% with 6 children	0.8	1
Total number of pregnancies that went beyond 20 weeks, median (range)	2.0 (1.0–6.0)	132
Number of pregnancies that went beyond 20 weeks		132
1, %	34.9	46
2, %	44.7	59
3, %	18.2	24
4, %	1.5	2
6, %	0.8	1
Father had OI, %	1	2
Father had any skeletal dysplasia, %	0	0

[a]These characteristics depict the values entered by the respondents at the time of the survey and not at the time of the pregnancy.

Abbreviations: cm – centimeter; kg- kilogram, BMI: body mass index, OI: Osteogenesis Imperfecta

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Table II:

Primary and Secondary Outcomes in pregnant women with OI

Outcome Type		Incidence in the general population in %	Observed incidence[a] in OI in % (N)[b]	95% CI for observed incidence in OI	p-value
Primary					
Maternal	Diabetes in pregnancy	6–7	13.3 (99)	7.0 – 19.6	**0.049**
	Hypertension in pregnancy	10	12.8 (99)	6.5 – 19.1	0.378
	Depression in pregnancy		9.1 (99)	3.5 – 14.7	0.499
	- Conception to birth	14–23			
	- Birth to 3 months	11–32			
	Preterm Birth rate (<37 weeks)	11.3	14.5 (101)	8.4 – 20.6	0.298
Fetal	Preterm premature rupture of membranes	3	5.6 (98)	1.8 – 9.4	0.173
	Need for transfusion	3	8.3 (100)	3.9 – 12.8	0.019
	Rate of cesarean section	32.7	68.5 (100)	59.9 – 77.1	**<0.001**
	Regional anesthesia use	61	28.5 (100)	20.3 – 36.7	**<0.001**
Delivery					
	NICU admission	5.7	19.0 (101)	11.9 – 26.0	**<0.001**
	Birth weight				
	- Low birth weight (<2500gm)	8.0	26.2 (100)	18.7 – 33.7	**<0.001**
	- Very low birth weight (<1500gm)	1.4	13.8 (100)	7.7 – 20.0	**<0.001**
	Rate of congenital defects	3	5.0 (101)	1.4 – 8.5	0.280
	Neonatal mortality (<28 days of life)	0.4	4.6 (102)	0.9 – 8.2	**0.026**
	Gestational age at delivery				
	- 40 weeks	33.6	14.7 (101)	8.1 – 21.3	**<0.001**
	- < 40 weeks	66.4	85.3 (101)	78.7 – 91.9	**<0.001**
	Breech presentation	4	12.6 (99)	6.4 – 18.8	**0.007**
Secondary	Miscarriage rate (clinically recognized <20weeks)	8–20	13.8 (126)	10.0 – 17.5	0.897

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Outcome Type		Incidence in the general population in %	Observed incidence[a] in OI in % (N)[b]	95% CI for observed incidence in OI	p-value
	Abortion rate (of all pregnancies)	21	4.0 (126)	1.9 – 6.2	**<0.001**
	Assisted reproductive technology use (in all births)	1.5	6.9 (101)	1.9 – 12.0	**0.035**
	Weight gain in pregnancy kilogram (average)	12	13.5 (83)	11.9 – 15.1	0.060
	Exercise in pregnancy	42	43.2 (101)	34.0 – 52.5	0.791
	Back pain in pregnancy	68.5	60.0 (100)	50.6 – 68.8	0.057
	Number of medications used in pregnancy (average)	4.2	1.8 (102)	1.5 – 2.0	**<0.001**
	Rate of breastfeeding				
	At 1 month	75.6	72.9 (102)	64.6 – 81.2	0.517
	At 6 months	51.4	34.8 (102)	26.0 – 43.6	**<0.001**

[a]: Weighted incidence as percentile

[b]: N is number of participants who answered the question

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Table III:

Neonatal Outcomes in pregnant women with OI

Characteristic	Value	Number of respondents recorded for a characteristic
Median birth weight, gm	2971.0	158
Mean birth weight, gm	2722.3	158
Birth weight <2500 gm, %	14.6	23
Birth weight <1500 gm, %	1.9	3
Median birth length, cm	48.3	139
Child affected with OI		167
No, %	47.3	79
Unknown, %	4.2	7
Yes, %	48.5	81
Child with any birth defects		164
No, %	95.2	158
Yes, %	4.8	8
Type of birth defect		164
Cleft lip/palate, %	1.2	2
Clubfoot, %	0.6	1
Congenital heart defect, %	1.2	2
Missing or undeveloped limbs, %	0	0
Phenylketonuria, %	0	0
Spina bifida, %	1.2	2
Other, %	1.2	2
NICU admission		165
Yes, %	16.4	27
No, %	83.6	138
Days in the NICU, median (range)	5 (1.0–98)	23
Child survive beyond 28 days		167
Yes, %	95.2	159
No, %	4.8	8

Abbreviations: grams, cm: centimeter, OI: Osteogenesis Imperfecta, NICU: neonatal intensive care unit

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Table IV-A:

OI in Pregnancy: Complications of OI

Characteristic	Value %	Number of responses recorded for a characteristic	Total number of respondents
Fractures during pregnancy	410.1	17	168
Feet/Toe	2.4	4	17
Upper arm	0.1	1	17
Forearm	2.4	4	17
Hands/Fingers	0	0	17
Hip	1.2	2	17
Upper leg	0	0	17
Lower leg	0.1	1	17
Spine	2.4	4	17
Fractures after pregnancy (within 2 months)	12.2	20	164
Feet/Toe	0.1	1	20
Upper arm	0	0	20
Forearm	0	0	20
Hands/Fingers	0	0	20
Hip	0.1	1	20
Upper leg	0	0	20
Lower leg	0	0	20
Spine	8.5	14	20
Other: rib/xiphoid process	2.4	4	20
Hospitalized during pregnancy due to OI	2.4	4	165
Back pain during pregnancy	57.2	95	167
Back pain worse during pregnancy	75.5	71	94
Back pain required medication	10.6	10	94
Back pain limiting activity/mobility	43.6	41	94

Abbreviations: OI: Osteogenesis Imperfecta

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Table IV-B:

OI in Pregnancy: Pregnancy characteristics and complications

Characteristic	Value	Number of respondents recorded for a characteristic	Total number of respondents
Length of pregnancy (wk), median (range)		168	168
Weight gain from pregnancy (kg), median (range)	12 (−12.7–39.0)	134	134
Pregnancy conceived using ART, %	9.5	16	168
Pregnancy conceived using IVF, %	5.4	9	168
Preimplantation genetic diagnosis for OI, %	4.8	8	168
Medications during pregnancy			
Calcium, %	21.2	35	135
Prenatal vitamin, %	89.1	147	165
Fish oil, %	6.1	10	165
Vitamin D, %	14.6	24	165
DHEA, %	3.6	6	165
Progesterone, %	7.9	13	165
Heparin or lovenox, %	3.1	5	163
Pain medication, %	9.1	15	165
Other, %	18.2	30	165
None, %	7.3	12	165
Exercise during 1st trimester of pregnancy, %	38.9	65	167
Exercise during 2nd trimester of pregnancy, %	33.3	56	168
Exercise during 3rd trimester of pregnancy, %	26	43	164
Health problems during pregnancy			
Diabetes, %	14.0	23	164
Diet controlled, %	69.6	16	23
Insulin, %	39.1	9	23
Oral medication, %	4.4	1	23
High blood pressure, %	12.7	21	165
Depression, %	9	15	166
Medication used, %	60	9	15
High blood pressure during delivery, %	38.1	8	21
Preterm labor, %	14.5	24	166
Hospitalized, %	50.0	12	24
Received magnesium sulfate, %	4.8	8	166
Received steroids for fetal lung maturity, %	7.3	12	165
Preterm premature rupture of membrane (< 36 wk), %	5.5	9	165

Abbreviations: y: years cm: centimeter kg: kilogram wk: weeks, ART: artificial reproductive technology, IVF: in vitro fertilization, OI: Osteogenesis Imperfecta, DHEA: Dehydroepiandrosterone

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Table IV-C:

OI in Pregnancy: Delivery and Postpartum Characteristics

Characteristic	Value	Number of responses recorded for a characteristic	Total number of respondents
Fetal presentation at term			
Cephalic, %	87	140	160
Breech, %	13	20	160
Delivery mode			
Vaginal, %	36	59	166
Forceps, %	4	7	166
Vacuum, %	4	7	166
Episiotomy, %	12	20	166
Cesarean section, %	65	108	166
Induction of labor, %	9	15	166
Anesthesia			
Regional (epidural/spinal), %	59	98	167
General, %	29	47	164
Received blood, %	10	17	166
Scar complications (Did scar open and need special treatment)			
Yes, %	45	5	106
No, %	95	102	106
Treated for postpartum depression, %	7	12	164
Breastfed or milk pumped postpartum, %	81	134	166
Total days in hospital median (range)	3.8 (0.0–14.0)	163	
Total days in the ICU median (range)	1.0 (1.0–4.0)	3	

Abbreviations: ICU: intensive care unit

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Table V-A:

Intrapartum characteristics by whether mother experienced fractures during pregnancy

Characteristic	Respondent with Fractures during Pregnancy N=17 % (n)	Respondent without Fractures during Pregnancy N=151 % (n)	p-value
Medication Use during Pregnancy	539.0 (20.0–152.19)		
Calcium	17.7 (3)	21.8 (32)	1.000
Vitamin D	17.7 (3)	14.3 (21)	0.718
Progesterone	11.8 (2)	7.5 (11)	0.628
Heparin and Lovenox	0 (0)	3.4 (5)	1.000
Bisphosphonate	5.9 (1)	3.3 (5)	0.585
Mobility Level during Pregnancy			
No restrictions	41.2 (7)	50.3 (76)	0.474
Some limitations	58.8 (10)	45.7 (69)	
Wheelchair dependent	0 (0)	4.0 (6)	
Exercised			
Prior to Pregnancy	47.1 (8)	43.0 (64)	0.746
During 1st Trimester	35.3 (6)	38.9 (58)	0.771
During 2nd Trimester	35.3 (6)	33.3 (50)	0.871
During 3rd Trimester	31.3 (5)	25.9 (38)	0.765
Any During Pregnancy	41.2 (7)	42.0 (63)	0.948
Hospitalized during pregnancy	5.9 (1)	2.0 (3)	0.355

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Table V-B:

Intrapartum characteristics and pregnancy outcomes by whether fetus had OI

Characteristic	Respondent with fetus with OI N=81	Respondent with fetus without OI N=79	p-value
Mother had fractures during pregnancy % (n)	11.25 (9)	7.69 (6)	0.446
Duration of pregnancy (weeks), mean (n, STD)	38.11 (81, 2.73)	38.02 (78, 2.15)	0.826
Weight gain from pregnancy (kg), mean (n, STD)	14.25 (68, 7.19)	12.02 (61, 7.08)	0.078
Birth weight (grams), mean (n, STD)	2503.1 (76, 1183.5)	2943.2 (76, 1036.9)	**0.016**
Child spent time in NICU (days) % (n)	17.3 (14)	15.6 (12)	0.773
Child lived at least 28 days after birth % (n)	95.1 (77)	96.2 (76)	1.000
Mother experienced depression % (n)	6.4 (5)	11.5 (9)	0.263
Mother treated for postpartum depression %(n)	8.8 (7)	5.3 (4)	0.395
Premature labor %(n)	16.7 (13)	14.1 (11)	0.657
Vertex presentation %(n)	89.6 (69)	84.4 (65)	0.338
Vaginal delivery %(n)	41.3 (33)	25.64 (20)	**0.038**
Cesarean delivery %(n)	60.0 (48)	73.08 (57)	0.081
Received an epidural %(n)	50.0 (40)	69.23 (54)	**0.014**
Received a transfusion %(n)	10.0 (8)	11.54 (9)	0.755
Length of Hospital Stay (days) mean (n, STD)	3.77 (79, 1.81)	3.82 (76, 2.31)	0.896
Child was breastfed or received breast milk %(n)	87.5 (70)	76.92 (60)	0.082
Abortion, mean (n, STD)	4.58 (63, 12.90)	5.05 (33, 14.72)	0.871
Miscarriage, mean (n, STD)	12.14 (63, 20.29)	11.31 (33, 20.95)	0.851

Abbreviations: STD: standard deviation, kg: kilograms, NICU: neonatal intensive care unit

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Table V-C:

Intrapartum characteristics and pregnancy outcomes by OI severity of Mother

Characteristic	OI Severity of Mother: Mild N=131	OI Severity of Mother: Moderate or Severe N=39	p-value
Received a transfusion, % (n)	10.1 (13)	10.81 (4)	1.000
Premature labor, % (n)	15.5 (20)	10.81 (4)	0.601
Mother experienced depression, % (n)	8.5 (11)	10.81 (4)	0.745
Mode of delivery			
Vaginal delivery, % (n)	43.4 (56)	8.11 (3)	**<0.001**
Cesarean section, % (n)	58.1 (75)	89.19 (33)	**<0.001**
Forceps, % (n)	3.9 (5)	5.41 (2)	0.653
Vacuum, % (n)	5.4 (7)	0 (0)	0.351
Induced labor, % (n)	10.9 (14)	2.70 (1)	0.194
Episiotomy, % (n)	14.7 (19)	2.70 (1)	0.049
Medication Use during Pregnancy			
Calcium, % (n)	21.4 (27)	20.51 (8)	1.000
Prenatal vitamins, % (n)	94.4 (119)	71.79 (28)	<0.001
Fish oil supplement, % (n)	6.4 (8)	5.13 (2)	1.000
Vitamin D, % (n)	16.7 (21)	7.69 (3)	0.202
DHEA, % (n)	3.2 (4)	5.13 (2)	0.627
Progesterone, % (n)	8.7 (11)	5.13 (2)	0.735
Pain Medications, % (n)	8.7 (11)	10.26 (4)	0.755
Heparin and Lovenox, % (n)	3.9 (5)	0 (0)	0.586
Bisphosphonate, % (n)	2.3 (3)	7.89 (3)	0.177
Mother had fractures during pregnancy, % (n)	10.8 (14)	7.89 (3)	0.765
Exercised			
Prior to Pregnancy, % (n)	46.5 (60)	35.90 (14)	0.273
During 1st Trimester, % (n)	42.2 (54)	28.21 (11)	0.136
During 2nd Trimester, % (n)	37.2 (48)	20.51 (8)	0.056
During 3rd Trimester, % (n)	30.7 (39)	10.81 (4)	0.019
Any During Pregnancy, % (n)	45.7 (59)	30.77 (12)	0.138
Hospitalized during pregnancy, % (n)	0.8 (1)	8.11 (3)	0.036
Duration of pregnancy (weeks), mean (n, STD)	38.78 (129,10.52)	37.76 (39, 3.42)	0.553
Weight gain from pregnancy $(kgs)^2$, mean (n, STD)	14.66 (103, 7.01)	8.66 (31, 5.36)	<0.001
Received an epidural, % (n)	58.1 (75)	60.53 (23)	0.853
Length of Hospital Stay (days), mean (n, STD)	3.75 (126, 2.18)	3.92 (37, 1.77)	0.675

Abbreviations: STD: standard deviation, kgs: kilograms, DHEA: dehydroepiandrosterone